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[Intervention Review]

5-FU for genital warts in non-immunocompromised individuals

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ABSTRACT

Background

Genital warts are common and usually are harmless but can be painful and psychologically burdensome. Several local treatments can be used, including topical 5-Fluorouracil (5-FU).

Objectives

To determine the effectiveness and safety of 5-FU topical treatment for genital warts in nonimmunocompromised individuals.

Search methods

Databases searched were Cochrane Central Register of Controlled Trials (The Cochrane Library 2009 Issue 3), MEDLINE (1966 to August 2009), EMBASE (until August 2009), LILACS (1982 to August 2009). The search had no language or publication restrictions.

Selection criteria

The review included randomised controlled trials (RCTs) among women, men, or both sexes, aged 18 years and older, comparing: 5-FU versus placebo or no treatment; 5-FU in any dose *v*ersus other isolated treatment, topical or systemic; 5-FU in any dose associated with other treatment versus placebo; 5-FU in any dose associated with other treatment versus other isolated treatment, topical or systemic; 5-FU in any dose associated with other treatment versus other associated treatment, topical or systemic.

Data collection and analysis

Two authors independently assessed trial quality and extracted data from the original publications.

Main results

Six trials involving 988 patients (645 women and 343 men) and reporting eight comparisons were found. Two studies reported withdrawals and dropouts, but none mentioned analysis by intention to treat (ITT). 5-FU presented better results for cure than placebo or no treatment (relative risk (RR) 0.39, 95% confidence interval (CI) 0.23 to 0.67), meta-cresol-sulfonic acid (MCSA) (RR 2.11, 95% CI 0.83 to 5.37), Podophylin 2%, 4% or 25% (RR 1.26, 95% CI 0.86 to 1.82). There were no statistical differences for treatment failure for 5-FU versus CO2 Laser (RR 0.69, 95% CI 0.43 to 1.11) versus 5-FU + INFα-2a (low dose) (RR 1.02, 95% CI 0.87 to 1.119). Worse results were found for 5-FU versus 5-FU + INFα-2a (high dose) (RR 10.78, 95% CI 1.50 to 77.36), and 5-FU + CO2 Laser INFα-2a (high dose) (RR 7.97, 95% CI 2.87 to 22.13).

Authors' conclusions

The reviewed trials were highly variable in methods and quality, and the evidence provided by these studies was weak. Cure rates with several treatments were variable, and although 5-FU presents therapeutic results that are inferior to those seen with 5-FU + Inf α-2a (high dose) and 5-FU + CO2 Laser + Inf α-2a (high dose), the treatment should not be abandoned. Topical treatment with 5-FU has a therapeutic effect; however, the benefits and risks have not been determined clearly and further studies are needed.

PLAIN LANGUAGE SUMMARY

5-FU for genital warts in nonimmunocompromised individuals

Genital warts is one of the most common types of sexually transmitted infection, with an estimated occurrence of about 32 million cases worldwide each year. The warts affect the genital area and cause such symptoms as itching, burning, discomfort, pain, or bleeding with intercourse. Because of the recurrence and the stigma associated with genital warts, frequently there are psychological burdens associated with the disease that possibly could become traumatic as feeling of shame, worry, fear, anger, and lowered self-esteem develop. Lesions can spread on one person and because they are easily spread between people, genital warts potentially can be a serious public health problem. There are many options for treating genital warts, but none so far are superior to the others. At this time, there is no available evidence that treatment efficiently eliminates genital warts or hinders its progression to malignancy. This review evaluated the effectiveness and safety of topical 5-FU for treatment of genital warts in nonimmunocompromised individuals. Evidence from the studies we reviewed showed that 5-FU had better results for cure than placebo or no treatment; MCSA; and Podophylin 2%, 4% or 25%. No statistical difference was found when 5-FU was compared with CO2 Laser treatment, and results were poor when 5-FU was compared with 5-FU + INFα-2a (high dose) or 5-FU + CO2 Laser INFα-2a (high dose). The weak point of this review was the great variability in the methods and quality of the studies that we included.

BACKGROUND

Genital Warts

Genital warts, also known as *condylomata acuminata* or venereal warts, is one of the most common types of sexually transmitted infection Mayo Clinic 2005 and primarily affect younger people. The disease usually is caused by human papillomavirus (HPV) genotypes 6 or 11, which normally are not involved with cancers. Association with HPV genotypes 16 and 18 can give rise to subclinical lesions associated with cervical intraepithelial neoplasia and squamous cancer Moore 2001.

As the name suggests, genital warts affect the moist tissues of the genital area. They may look like small, flesh-coloured bumps or have a cauliflower-like appearance. Genital warts may be as small as 1 to 2 millimetres in diameter - smaller than the width of a ballpoint pen refill - or may multiply into large clusters Mayo Clinic 2005.

In the United Kingdom in 1998, there were 111,000 reported new cases in clinics of genitourinary medicine Lamagni 1998, and In the United States, approximately 20 million people are infected with HPV. For most people, HPV infection clears up spontaneously; however in some people, certain high-risk types of HPV, if unrecognised and untreated, can lead to cervical cancer. Approximately 1 million cases of genital warts occur each year in the United States and an estimated 32 million cases occur worldwide Merck's 2006.

Human papillomavirus types 6 or 11 are not linked to cervical cancer, but they can cause abnormal Papanicolaou smears, which then lead to additional tests and unnecessary worries about cancer Merck's 2005. In women, genital warts can appear on the vulva, the walls of the vagina, the perianal area, and the cervix. In men, they may be found on the tip or shaft of the penis, the scrotum, or the anus. They also can develop in the mouth or throat of a person who has had oral sexual contact with an infected person. The signs and symptoms of genital warts include tiny, grey, pink, or red swellings in the genital area that grow quickly and cause localized Itching and burning, discomfort, and pain or bleeding with intercourse. Several warts close together take on a cauliflower shape. Although genital warts can be treated with medications and surgery, they are a serious public health concern as human papillomavirus has been associated with cervical cancer and other types of genital cancers Mayo Clinic 2005.

Biology and Natural History of HPV

Biology

Human papillomavirus (of which 80 types have now been characterised and several others reported) are DNA viruses which infect epithelial cells. Viral replication takes place only in fully differentiated epithelium, and the subsequent proliferation results in a clinically evident warty papule or plaque. The clinical appearance of warts is variable and depends to some extent on the type of HPV involved and the anatomical site. It can also remain dormant within epithelial cells without visible disease. Any epithelial surface can be affected and different types of HPV tend to favour particular anatomical sites, but the most common infections are with HPV type 2 on the hands and feet. Human papillomavirus types 1, 4, 27, and 57 are also frequently found in common warts. Plane or flat warts, which are clinically distinct from common warts and usually occur on the distal limbs and face, are caused by HPV types 3 or 10 Sterling 1998.

Human papillomaviruses are small double-stranded DNA viruses of 7,900 base pairs. They belong to the family of Papovaviridae. More than 100 types have been detected, based on differences in their DNA. They infect the epithelium and can be divided into cutaneous and mucosal types. Mucosal types can infect the genital tract, including the vulva, vagina, cervix, and perianal area. They can be subdivided into high-, intermediate-, and low-risk types depending on the type of lesions they produce and their association with malignancy. Clinical presentations of HPV infection include genital warts, cervical intraepithelial neoplasia (CIN), and invasive cervical cancer, although most infections are asymptomatic. Fifteen high- and intermediate-risk types (16, 18,31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are associated with CIN and squamous carcinoma and adenocarcinoma of the cervix, low-risk types (mostly types 6, 11) are commonly detected in genital warts Munoz 2003.

The genome of papillomaviruses is divided in seven early (E) and two late (L) regions. The L1 and L2 regions code for the viral capsid protein (the outer shell of the virus) whereas the E (E1 to E7) genes are involved in viral replication and cell transformation. When HPV is associated with a benign lesion, the viral genome replicates separately to the host cell's DNA. In contrast, in malignant lesions, the HPV DNA is integrated into the host cell's chromosomes. After integration a series of events leads to deregulation of the E6 and E7 genes of HPV. The products of the viral E6 and E7 genes inactivate the host cell cycle regulators p53 and pRB leading to the cellular transformation process and CIN and cervical cancer Koliopoulos 2006.

Clinically, genital warts affect the moist tissues of the genital area. They may look like small, flesh-coloured bumps or have a cauliflower-like appearance (condylomata acuminata). Genital warts may be clinically inapparent or as small as 1 to 2 millimetres in diameter or may multiply into large clusters Mayo Clinic 2005. They can also develop in the mouth or throat of a person who has had oral sexual contact with an infected person.

Human papillomavirus-associated disease is not limited to adults and adolescents. Genital warts have been reported in children born from mothers with condylomata acuminata, although such lesions are rare Schwartz 1987. Much more serious is the inoculation of HPV into the upper respiratory tracts of infants born from affected mothers. Infected infants may develop respiratory papillomatosis. Retrospectively, the presence of maternal condylomata acuminata has been reported in 55 to 65 percent of children with respiratory papillomatosis Schwartz 1987. Although HPV infection does not appear to be associated with increased risk of spontaneous abortion, prematurity, or other prenatal complications, its etiologic association with respiratory papillomatosis in infants and children seems indisputable Byrne 1987.

The specifics of maternal-to-child transmission remain unknown and are made unclear because maternal lesions easily can be overlooked. Transmission typically follows vaginal delivery, but has also been documented after cesarean section Shah 1986. Estimates of the rate of transmission have been quite variable and are based on limited data. Some authors suggest that HPV, as well as herpes simple virus and cytomegalovirus, can be transmitted during childbirth more frequently by vaginal secretion aspiration

than transplacentally Smith 1991, Sedlacek 1989, Roman 1986. The lifetime risk of developing laryngeal papillomatosis for children born of mothers with condylomata acuminata has been estimated as about 1 in 30 Schwartz 1987. Steinberg 1988, however, estimated a rate of one infant case per 1,000 infected mothers. This means that if disease prevalence was about 20 percent among the approximately 5 million annual pregnancies in the United States and Western Europe, about 1,000 affected babies could be expected each year. This may seem like a small number, but its importance is magnified by the devastation associated with juvenile respiratory papillomatosis, which lacks a consistently curative treatment; for these children, recurrence is the rule and lifelong morbidity and multiple operations result Schwartz 1987.

The child with respiratory papillomatosis typically presents between two and three years of age, although the age of onset varies considerably and extends into adolescence. Papillomatosis follows an extremely variable course. Underlying factors that determine whether the disorder is benign or aggressive are not yet clear. Hoarseness and respiratory distress are the usual presenting features. The larynx, trachea, and pulmonary tree all may be affected and the larynx may become completely obstructed Steinberg 1988, Kashima 1987, Brodsky 1987. Although one study showed no associated mortality among patients with a follow-up time ranging from 4 to 45 years Byrne 1987, pulmonary involvement by papillomatosis may be severe Christiansen 1984. Genital warts may increase in size during pregnancy Oriel 1971, complicating delivery and posing a risk of laryngeal papillomatosis in neonates delivered vaginally Kashima 1996, Onnez 1995, Fletcher 1991, Oriel 1971. The role of cesarean delivery is unclear in preventing laryngeal papillomatosis Kashima 1996, Onnez 1995, so pregnant patients and those planning pregnancies should be encouraged to undergo treatment. The more important clinical manifestation of the infection of the larynx for HPV is the laryngeal papilloma, that it is fit in the category of papillomatosis respiratory recurrent. Currently, this disease is divided in two distinct groups, one that appears in childhood and youth and the other that appears in adulthood Aaltonen 2002. Papilomas appearing in childhood and youth is associated with HPV transmitted vertically from a mother with active or latent anogenital infection. More than 30% of mothers with condylomas who gave birth vaginally had children who developed youthful laryngeal papillomatosis Conejo 2001. This illness occurs more commonly in first-born children and in the children of young mothers who had genital warts and who give birth vaginally. Cases of children with laryngeal papillomatosis who have been born by caesarian section are rare. The virus stimulates the proliferation of papillomas in the airways, usually in the larynx. The progression of papillomas is slow, generating progressive respiratory symptoms, dysphonia, and persistent cough Vancurova 2002, Conejo 2001.

Youthful laryngeal papilloma occurs equally in both sexes, and of greatest concern is the dissemination of the virus into the bronchotracheal tree where it evolves into pulmonary papillomatosis and often results in uncontrollable and fatal infection.

Although it is not common for papilloma of the larynx to become malignant, it occurs in about 37% of cases Aaltonen 2002. Treatment is based on the surgical removal of the polyps with Co2 laser. Conventional surgery is far from being the best choice for treatment due to the viral etiology of the illness. A-Interferon may be used, especially for children, in whom larynx papillomatosis is more aggressive than among adults, with frequent recurrence and possible migration of the virus into the lower respiratory tract. The objective of treatment is to keep airways open and retain the quality of the voice Aaltonen 2002. Adult-occurring papillomas of the larynx appear in individuals with more sexual partners and greater frequency of orogenital contact. The hypothesis of orogenital transmission is that in genital as well as in laryngeal papillomatosis, type 6 virus is the most frequently occurring type. The transition area of cuboidal to cylindrical epithelium in the larynx and the cervix can favour the occurrence of HPV, and the similarity between these regions seems to favour infection of the epithelium of the larynx Aaltonen 2002, Vancurova 2002, Butel 2000.

Epidemiology of HPV

The spread of the HPV infection occurs primarily through sexual contact. Risk factors include a high number of sexual partners, the presence of genital warts on sexual partners, a history of sexually transmitted infections, smoking, the use of oral contraceptives, high parity (number of children), and immunosuppression. The estimated prevalence of genital warts in the United States is 1 percent and in Europe it varies between 0.75 percent and 3 percent Koliopoulos 2006, Sanclemente 2002, Mougin 2001.

It has been established that HPV is a factor in but is not solely sufficient to cause invasive cervical cancer. It is the most common sexually transmitted infection worldwide and studies done in developed countries suggest that an estimated 50 to 80 percent of sexually active women are infected at least once in their lifetime. Women are usually infected with HPV in their teens, 20s, or early 30s, although these infections are typically transient or become undetectable over time PATH 2005, Ho 2002, Koutsky 1998.

The rate of infection by any HPV type among sexually active young women within three years was 44% in a recent study Woodman 2001. Women under 25 to 30 years have higher rates of infection although a second peak has been described in postmenopausal women. Experimental, clinical and epidemiological evidence shows that HPV is a virus of predominantly sexual transmission and that a great number of people will be infected with one or more forms throughout their life Gibbs 2006, Lamagni 1998. In 8 to 14% of the cases of genital warts, the person has been infected with more than one type of HPV Sykes 1995.

Treatment

The ideal treatment for any disease, including genital warts, should be simple, cheap, effective, and free of side effects. Available treatments for condyloma include bichloracetic or trichloroacetic acid, CO2 Laser, podophyllin, podophyllotoxin, 5-fluorouracil, cryotherapy, topical or systemic immunotherapy, surgical excision or curettage and cautery. Some of these treatment options, such as topical or systemic immunotherapy, surgical excision, curettage and cautery are expensive, generally carry a higher risk of side effects, are more uncomfortable, and require specialised care.Gibbs 2006.

5-FLUOROURACIL

5-Fluorouracil is a fluorinated pyrimidine antimetabolite that functions as an antineoplastic agent by blocking DNA synthesis.

Once administered, the drug is concentrated especially on neoplastic tissue Oliveira 2002, Machado 2000, Murad 1996. Although the United States Food and Drug Administration (FDA) has not approved the use of 5-FU cream for genital warts, it is being used by physicians based on results from uncontrolled clinical trials and a few RCTs, as found in this review. This antimetabolite drug is most commonly used to treat a variety of skin neoplasms and precancerous lesions, such as actinic keratosis. It has been used by clinicians for treating urethral condylomata since the early 1990s. It can also be used on more routine anogenital condylomata, apparent or subclinical, with good effect Dyment 1996.

Fluorouracil for treatment of genital warts has been used as a cream or solution of between 1% and 5% Adler 1985, Davis 1989, Pride 1990 and has been tried with variable results as an adjuvant to laser therapy in severe papillomavirus-associated vulval disease Dyment 1996, Reid 1990. Anderson 1985 suggested using 5-FU as a 5% cream, which should be applied directly to the wart daily and covered with a waterproof dressing; however, some authors have claimed success using fluorouracil without a covering in the treatment of plane warts.

There are no significant differences in the literature between the side effects presented by topical 5-FU and any other treatment for genital warts. Thus, this review looked for explanations why 5-FU has been missed as an option for genital warts as a serious public health problem.

To see a summary of the mechanisms of action of other treatments used for genital warts, see Table 1.

OBJECTIVES

To determine the effectiveness and safety of topical 5-FU as a treatment for genital warts in non-immunocompromised individuals.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were included in this review

Types of participants

Women and men aged 18 years or more who were nonimmunocompromised and who presented with clinical or subclinical genital warts.

Types of interventions

The included studies have analysed the following interventions:

- Topical 5-FU in any dose versus placebo or no treatment
- Topical 5-FU in any dose versus other isolated treatment, topical or systemic.
- Topical 5-FU in any dose associated with other treatment versus placebo.
- Topical 5-FU in any dose associated with other treatment versus other isolated treatment, topical or systemic.
- Topical 5-FU in any dose associated with other treatment versus other associated treatment topical or systemic.

Types of outcome measures

The outcomes measured were:

Primary Outcomes

- Patient or warts response: cure or partial improvement
- Recurrence rate

Secondary Outcomes

- Local reactions
- Other related adverse events

Search methods for identification of studies

The search strategy of studies for this review was performed by the Research Assistant of the Center Cochrane of Brazil, from the following terms (Genital Warts, Condylomata Acuminata, Papillomavirus Human, Human Papillomaviruses, 5 Fluorouracil, 5-Fluorouracil, 5 Fluorouracil, 5 FU, Antimetabolites, Antineoplastic, and Immunosuppressive Agents), and had no language or date restrictions.

Full search strategy from terms below is as follows:

1. “CONDYLOMATA ACUMINATA” [ALL FIELDS]

2. “GENITAL WARTS” [ALL FIELDS]

3. “GENITAL WART” [ALL FIELDS]

4. “WART, GENITAL” [ALL FIELDS]

5. “WARTS, GENITAL” [ALL FIELDS]

6. “VENEREAL WARTS” [ALL FIELDS]

7. “VENEREAL WART” [ALL FIELDS]

8. “WART, VENEREAL” [ALL FIELDS]

9. “WARTS, VENEREAL” [ALL FIELDS]

10. or/#1 #9

11. "PAPILLOMAVIRUS, HUMAN” [ALL FIELDS]

12. “HUMAN PAPILLOMAVIRUSES” [ALL FIELDS]

13. “PAPILLOMAVIRUSES, HUMAN” [ALL FIELDS]

14. “PAPILLOMAVIRUS INFECTIONS” [ALL FIELDS]

15. "HUMAN PAPILLOMAVIRUS” [ALL FIELDS]

16. “HUMAN WART VIRUS, INFECTIOUS [ALL FIELDS]

17. “INFECTIOUS HUMAN WART VIRUS” [ALL FIELDS]

18. “PAPILLOMA VIRUS, HUMAN” [ALL FIELDS]

19. “HUMAN PAPILLOMA VIRUS” [ALL FIELDS]

20. “HUMAN PAPILLOMA VIRUSES” [ALL FIELDS]

21. “PAPILLOMA VIRUSES, HUMAN” [ALL FIELDS]

22. or/# 11# 21

23. “SEXUALLY TRANSMITTED DISEASES, VIRAL [ALL FIELDS]

24. “SEXUALLY TRANSMITTED DISEASE, VIRAL” [ALL FIELDS]

25. “VIRAL SEXUALLY TRANSMITTED DISEASE” [ALL FIELDS]

26. “VENEREAL DISEASES, VIRAL” [ALL FIELDS]

27. “VIRAL VENEREAL DISEASES” [ALL FIELDS]

28. “DISEASE, VIRAL VENEREAL” [ALL FIELDS]

29. “DISEASES, VIRAL VENEREAL [ALL FIELDS]

30. “VENEREAL DISEASE, VIRAL” [ALL FIELDS]

31. “VIRAL VENEREAL DISEASE” [ALL FIELDS]

32. “VIRAL SEXUALLY TRANSMITTED DISEASES” [ALL FIELDS]

33. or/#23 #32

34. “FLUOROURACIL” [ALL FIELDS]

35. “5-FLUOROURACIL” [ALL FIELDS]

36. “5 FLUOROURACIL” [ALL FIELDS]

37.“FLUORURACIL” [ALL FIELDS]

38. “5-FU” [ALL FIELDS]

39. “5FU” [ALL FIELDS]

40. “FLUOROURACIL POTASSIUM SALT” [ALL FIELDS]

41. “ADRUCIL” [ALL FIELDS]

42. “EFUDIX” [ALL FIELDS]

43. “FLUOROPLEX” [ALL FIELDS]

44. “FLUOROURACIL MONONITRATE” [ALL FIELDS]

45. “FLUOROURACIL MONOPOTASSIUM SALT” [ALL FIELDS]

46. "FLUOROURACIL MONOSODIUM SALT” [ALL FIELDS]

47. “ANTIMETABOLITES” [ALL FIELDS]

48. “ANTIMETABOLITES, ANTINEOPLASTIC” [ALL FIELDS]

49. “IMMUNOSUPPRESSIVE AGENTS” [ALL FIELDS]

50. or/# 34 #49

51. RANDOMIZED CONTROLLED TRIAL [PUBLICATION TYPE]

52. CONTROLLED CLINICAL TRIAL [PUBLICATION TYPE]

53. RANDOMIZED CONTROLLED TRIALS [MESH TERMS]

54. RANDOM ALLOCATION [MESH TERMS]

55. DOUBLE BLIND METHOD [MESH TERMS]

56. SINGLE BLIND METHOD [MESH TERMS]

57. CLINICAL TRIAL [PUBLICATION TYPE]

58. CLINICAL TRIALS [MESH TERMS]

59. CLINICAL* [TEXT WORD]

60. TRIAL* [TEXT WORD])

61. SINGLE* [TEXT WORD]

62. DOUBLE* [TEXT WORD]

63. TREBLE* [TEXT WORD]

64. TRIPLE* [TEXT WORD]

65. PLACEBOS [MESH TERMS]

66. PLACEBO* [TEXT WORD]

67. RANDOM* [TEXT WORD]

68. RESEARCH DESIGN [MESH TERMS]

69. COMPARATIVE STUDY [MESH TERMS]

70. EVALUATION STUDIES [MESH TERMS]

71. FOLLOW-UP STUDIES [MESH TERMS]

72. PROSPECTIVE STUDIES [MESH TERMS]

73.CONTROL* [TEXT WORD]

74. PROSPECTIV* [TEXT WORD]

75. VOLUNTEER* [TEXT WORD]

76. or/#51-#75

77. #10 and # 22 and # 33 and # 50 # and 76

The references of the articles identified were hand searched for other relevant articles.

The following databases were searched: Cochrane Central Register of Controlled Trials (The Cochrane Library 2009 Issue 3), MEDLINE (from 1966 to July 2009), EMBASE (until July 2009) and LILACS (until July 2009**)**

We tried contacting two authors Table 2 in order to obtain additional data and ask about other relevant published or unpublished studies, but we had no reply, perhaps due to the publication date.

We also tried contacting the manufacturer of 5-FU in the pharmaceutical industry Table 3, in order to obtain more details about other studies, but we had no reply

The following journals were hand searched for articles and conferences proceedings:

RBGO - Revista Brasileira de Ginecologia & Obstetrícia (Rev Bras Ginecol Obstet.)

JB - DST - Jornal Brasileiro de Doenças Sexualmente Transmissíveis (DST - J Bras Doenças Sex Transm)

Annals of Congresses of the listed societies below had been used for attainment of registers of lectures and conferences:

Febrasgo - Brazilian Federation of the Associations of Gynecology and Obstetrics

FIGO - International Federation of Gynecology and Obstetrics

Data collection and analysis

The review was carried out in four stages:

First stage (Study Selection) -

One reviewer (CSB) assessed the titles and abstracts of the literature search to determine whether they met the eligibility criteria, and when there were any doubts the full text of the articles were retrieved. Another reviewer (HS) received the search results and the articles selected by CSB in order to identify if any articles had been missed. As there was no disagreement between both reviewers, the third reviewer (ANA) was not consulted in this stage. The selection process was not blinded.

Second stage (Assessment of Study Quality) -

Two reviewers (CSB, HS) assessed independently the validity (the likelihood of selection, performance, attrition and detection bias) of the selected studies. There were no disagreements between both reviewers.

The methodological quality of the trials included in this review was assessed using the criteria described in the Cochrane Handbook Clarke 2002, which is based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment Schulz 1995.

The categories are defined below:
A - Low risk of bias (adequate allocation concealment)
B - Moderate risk of bias (some doubt about the results)
C - High risk of bias (inadequate allocation concealment)

The quality of each trial concerning the criteria of quality specified by Schulz 1995, which measures a wider range of factors that impact on the quality of the trial.
In particular the following factors were studied:

Minimisation of selection bias:
a) Was the randomisation procedure adequate?
b) Was the allocation concealment adequate?

Minimisation of attrition bias:
a) Were withdrawals and dropouts completely described?
b) Was analysis done by intention-to-treat?

Minimisation of detection bias:
a) Were outcome assessors blind to the intervention?

This classification was used on the basis of a sensitivity analysis. Additionally, we explored the influence of individual quality criteria in a sensitivity analyses.

Third stage (Data Collection) -

- Interventions and outcomes were extracted independently by reviewers (CSB, HS, ANA, EMK) using a data extraction form (Appendix 1) which includes the following information:
- General information: published/unpublished, title, authors, reference/source, country, language for publication, year of publication, duplicated publication, sponsoring.
- Trial characteristics: design, duration, randomisation (and method), allocation concealment (and method), blinding (patients, outcome assessors).
- Patients: sampling (random/consecutive), exclusion criteria, total number and number in comparison groups, sex, age, withdrawals/losses in the follow-up (reasons/description), subgroups.
- Intervention(s): intervention, control, additional treatments.
- Outcomes: above specified outcomes, any other assessed outcomes, other events, length of follow-up, quality of outcomes reporting.
- Results: for outcomes as specified (including a measure of variation), if necessary converted to the effective measures specified below; intention-to-treat analysis.
- Differences in data extraction were arranged by consensus among reviewers referring back to the original article.

Fourth stage (Data Analysis) -

Data on 5-FU performance were analysed.

Data were entered into RevMan by one reviewer (CSB), and were included in meta-analysis when there they were sufficient in quality and were sufficiently similar. Dichotomous data were expressed as relative risks (RRs). When clinically significant, dichotomous data were converted to number needed to treat (NNT). Heterogeneity was tested for using the Chi^2 statistic with significance being set at $P < 0.1$. Quantification of the effect of heterogeneity was assessed by the I^2statistic, ranging from 0-100% including its 95% confidence interval Higgins 2002. The I^2 demonstrates the percentage of total variation across studies due to heterogeneity and was used to judge the consistency of evidence. Possible sources of heterogeneity were assessed by sensitivity and subgroup analyses as described below. Small study bias was tested for using the funnel plot technique.

Subgroup Analysis

Subgroups analysis were performed by gender, age, drug concentrations and types of condyloma present if CA, CP or both CA and CP .

Sensitivity Analysis

We performed sensitivity analyses in order to explore the influence of the following factors on effect size:
1. Repeating the analysis excluding unpublished studies (if there were any).
2. Repeating the analysis taking account of study quality, as specified above.
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
4. Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results was also tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistic models (fixed and random effects models).

RESULTS

Description of studies

Result of the search

One hundred sixty-four (164) articles were obtained in the search of which 132 were excluded by headline or abstract analysis and 32 were evaluated in more details. From these 32 studies, 26 were excluded and 6 were selected to compose this revision. See Excluded studies table, and Included studies table, respectively

Included studies

Six (6) studies met all inclusion criteria and were included in this review. See Included studies table

Excluded studies

Twenty six (26) studies were excluded after examining the entire text. The studies were excluded for more than one reason, the commonest being the absence of one or more groups of comparison, or the absence of method of randomised allocation, or for not being an RCT. See Excluded studies table

Risk of bias in included studies

Methodological quality

One of the six included studies has been classified as having low risk of bias (Syed 2000). The five remaining studies were classified as being of moderate risk of bias in view that the quality criteria were not clear (Botacini 1993; Carpinelo 1988; Relakis 1996; Wallin 1977: Weismann 1982)

Minimisation of selection bias

Only one study adequately described the procedure of randomisation (Wallin 1977) and in remained five studies there were no mention for that procedure. The allocation occultation was not mentioned in any of the six enclosed studies

Minimisation of attrition bias

One study adequately described the procedure of randomisation Wallin 1977 and in the remaining five, only two Wallin 1977; Syed 2000 mentioned the allocation occultation although it was not clearly described, and in three studies there were no mention of that procedure.

Minimisation of detection bias

Two studies mentioned that the participants were blind Syed 2000; Weismann 1982 while the other 4 did not make reference to the blinding neither of appraisers nor of participants.

Effects of interventions

Interventions in this review observed the following effects:

1. Cure (Botacini 1993, Wallin 1977, Relakis 1996, Syed 2000, Weismann 1982),

2. Partial response / improvement (Botacini 1993, Syed 2000, Weismann 1982)

3. Treatment failure / resistance (Botacini 1993, Wallin 1977, Syed 2000, Weismann 1982),

4. Side effects (Botacini 1993, Relakis 1996, Syed 2000),

5. Lesion recurrence (Carpinelo 1988, Wallin 1977, Relakis 1996)

Intervention results are presented separately for each comparison as follows: (5-FU versus placebo, 5-FU 5% versus Meta-cresol-sulfonic Acid, 5-FU 5% versus Podophylin, 5-Fu 5% versus CO2 Laser, 5-FU 5% versus 5-FU 5% plus Interferon α-2a (Low dose), 5-FU 5% versus 5-Fu 5% plus Interferon α-2a (High dose), 5-FU 5% versus 5-FU 5% plus Laser de CO2 plus Interferon α-2a (High dose) and CO2 Laser versus CO2 Laser plus 5-FU 5%)

1. 5-FU versus placebo

Botacini et al, 1993, used a 5-FU 5% gel. Seventy-four female patients were allocated in 5-FU 5% Group and sixteen female patients were allocated for Placebo Group.

The results in order to evaluate the outcomes in 5-FU Group were: cure, 52 patients; Partial response/ improvement, 7 patients; no response / treatment resistance, 5 patients, and in Placebo Group: Cure, 5 patients, Partial response/ improvement, 1 patient and no response / treatment resistance, 10 patients.

Syed at al, 2000, used a 5-FU 1% gel. Thirty patients were allocated in each group. Three hundred and twelve genital warts were observed being 162 in 5-FU Group and 150 in placebo Group.

The results in 5-FU Group were: cure, 25 patients, side effects, 2 patients; lesion recurrence, 2 patients, and in Placebo Group - cure, 4 patients; side effects, 1 patient; lesion recurrence, 1 patient.

Concerning warts response, the following results were observed in 5-Fu Group, cure - 141 lesions and in Placebo Group, 21 lesions.

The authors conclude that 5-Fu 1% presents low index of side effects and it is safe and well tolerated for the vaginal treatment of condyloma.

Weissmann et al, 1982, evaluated a 5-FU 0,5% gel. Fifty-nine patients were selected for the study of which 30 were male (14 in 5-FU Group and 16 in Placebo Group) and 29 were female (16 in 5-FU Group and 13 in Placebo Group)

The results for 5-FU Group were: cure, 18 patients (10 male and 8 female) improvement, 6 patients (2 male and 4 female) no response, 6 patients (4 male and 2 female) for the Placebo Group: cure, 8 patients (4 male and 4 female) improvement, 4 patients, (1 male and 3 female), and no response, 17 patients (8 male and 9 female).

The authors related fast burning as a side effect for all patients in the place of the 5-FU application

Laboratorial examinations (haemoglobin evaluation, leukocytes, platelets, alanine-transferasis IgG, IgA, IgM and creatinine) were related but had no significant alterations.

Meta-analysis:
Data from these 3 studies Botacini 1993; Syed 2000; Weismann 1982 could be pooled but demonstrated heterogeneity (I^2 = 62%).

[RR 0.39 (95% IC, 0.23, 0,67)]. NNT = 2

2. 5-FU 5% versus Meta-cresol-sulfonic Acid

In this comparison Botacini et al, 1993, used a 5-FU 5% gel versus Meta-Cresol-Sulfonic Acid, and 74 female patients were allocated to 5-FU Group and 9 patients to the Meta-Cresol-Sulfônic Acid (MCSA) Group.

The results for the 5-FU Group were: cure, 52 patients, partial response, 7 patients, and no response, 15 patients, and for the MCSA Group: cure, 3 patients, partial response, 1 patient, and no response, 5 patients.

3. 5-FU 5% versus Podophylin

Botacini et al, 1993, evaluated 5-FU gel versus two chemical preparations of Podophylin, to 2% and to 4%. Seventy-four patients used 5-FU 5% gel and 5 patients used Podophylin 4% and 40 patients used Podophylin 2%.

The results in the 5-FU Group were: cure, 52 patients, partial response, 7 patients, no response, 15 patients while in the Podophylin Group 4% were: cure, 3 patients, partial response, 1 patient, and no response, 1 patient, and in the Podophylin 2% Group: cure, 19 patients; partial response, 5patients; and no response, 16 patients.

Wallin et al, 1977, used 5-FU 5% gel and a Podophylin 25% gel. Forty-two male patients were selected for the study, 20 were allocated in the 5-FU Group and 22 in the Podophylin Group.

There were 2 withdrawals in 5-FU Group and 3 in Podophylin Group.

The results were evaluated after 4 and 9 weeks. After 4 weeks, for the 5-FU Group, the results were: cure, 10 patients; and for the Podophylin Group: cure, 11 patients. After 9 weeks, in the 5-FU Group the results were: cure, 6 patients, and in the Podophylin Group: cure, 10 patients.

Meta-analysis:
Data from two studies (Botacini 1993; Wallin 1977) could be pooled and did not demonstrate heterogeneity ($I^2 = 32\%$). [RR 1.26 (95% IC, 0.86, 1,82)]. NNT = 6

4. 5-FU 5% versus CO2 Laser

Relakis, 1996, performed 3 study groups that were constituted on the basis of the presence of Condyloma Acuminatum (CA), Condyiloma Plain (CP) or both condyloma, acuminatum or plan, in the same patient. A 5-FU gel was used.

The only studied outcome was Treatment Failure.

Lesion Recurrence observed in the first year after treatment was considered as Treatment Failure

Lesion Recurrence occurred in 5-FU 5% Group at 3, 6 and 9 months.

Side Effects were observed in 11% of the patients treated with 5-FU

In CA group, 33 males patients were treated with 5-FU 5% while 12 patients were placed in the CO2 Laser Group.

Treatment Failure in 5-FU Group was: 8 patients and in CO2 Laser Group: 4 patients,

In CP Group, 156 male patients were treated with 5-FU 5% while 39 patients were placed in the CO2 Laser Group.

Results in 5-FU 5% Group were: 29 patients and in CO2 Laser Group, 12 patients,

In Ca + CP Group, 29 male patients were treated with 5-FU 5% while 20 patients were placed in the CO2 Laser Group.

Results in 5-FU 5% Group were: 14 patients and in CO2 Laser Group, 30 patients,

5. 5-FU 5% versus 5-FU 5% plus Interferon α-2a (Low Dose)

In this evaluation Relakis et al, 1996, performed 2 study groups, one in which were dealt with 5-FU 5% and another one where the patients had been dealt with 5-FU 5% + Interferon α-2a (INF?-2a) (low dose).

The only studied outcome was Treatment Failure.

Lesion recurrence observed during the first year after treatment was considered as Treatment Failure.

Lesion recurrence occurred in the 5-FU 5% Group in months 3, 6 and 9.

Side effects had been observed in 11% of the patients dealt with 5-FU 5%

In CA group 33 male patients were treated with 5-FU 5% while 27 patients were placed in the 5-FU 5% Group + INFα-2a (low dose)

Results in the 5-FU 5% Group were - 8 patients and in the 5-FU 5% + INFα-2a (low dose) Group - 7 patients.

In CP group, 156 male patients were treated with 5-FU 5% while 18 patients were placed in 5-FU 5% + INFα-2a (low dose) Group

Results in the 5-FU 5% Group were - 29 patients and in the 5-FU 5% + INFα-2a (low dose) Group - 2 patients.

In CA + CP Group, 29 male patients were treated with 5-FU 5% while no patients were included in the 5-FU 5% + INFα-2a (low dose) Group.

Results in the 5-FU 5% Group were - 14 patients

6. 5-FU 5% versus 5-FU 5% + Interferon?-2a (High dose)

In this evaluation Relakis et al, 1996, compared 5-FU 5% versus 5-FU 5% + Interferon α-2a (High Dose). Patients were allocated in 2 study groups, one in which the patients were dealt with 5-FU 5% and another one where the patients had dealt with 5-FU 5% + Interferon α -2a (INF? -2a) (high dose)

In CA Group, 33 male patients were treated with 5-FU 5% and there was no comparison with the 5-FU 5% + INF α -2a (high dose) treatment.

The outcome studied was Treatment Failure, and results in the 5-FU 5% Group were 8 patients.

In CP Group, 156 male patients were treated with 5-FU 5% while 58 patients were placed in the 5-FU 5% + INF α - 2a (high dose) Group.

The outcome studied was Treatment Failure and results in the 5-FU 5% Group were - 29 patients and in the 5-FU 5% + INF? -2a (high dose) Group - 1 patient.

In Ca + CP Group, 29 male patients were treated with 5-FU 5% and there was no treatment with 5-FU 5% + INFα-2a (high dose).

The outcome studied was treatment failure, and the results in the 5-FU 5% Group were 14 patients

Lesion Recurrence observed during the first year after treatment was considered as Treatment failure

Lesion recurrence occurred in the 5-FU 5% Group in months 3, 6 and 9.

Side effects were observed in 11% of the patients dealt with 5-FU 5%.

7. 5-FU 5% versus 5-FU 5% + Laser CO2+ Interferon?-2a (INFα-2a) (High dose)

In this evaluation Relakis et al., 1996, compared the use of 5-FU 5% versus 5-FU 5% + Laser CO2+ Interferon? -2a (INF?-2a) (high dose) . Patients were divided in three study groups based on the presence of condyloma Acuminatum (CA), condyloma Plain (CP) or both CA + CP in the same patient.

Each study group was again divided in two new groups according to the treatment applied. One in which patients were dealt with 5-FU 5% and another one where the patients were dealt with 5-FU 5% + Laser CO2+ Interferon α -2a (INFα-2a) (high dose)

For all 3 groups, divided in accordance with the type of condyloma, the only outcome studied was Treatment Failure.

In CA group, 33 male patients were treated with 5-FU 5% and 30 male patients were treated with 5-FU 5% + Laser of Co2 + INF α -2a (high dose)

Results in the 5-FU 5% Group were - 8 patients and in the 5-FU 5% + Laser of Co2 + INF α -2a (high dose) there were no patients, no treatment failure.

In CP group, 156 male patients were treated with 5-FU while 20 male patients were placed in 5-FU 5% + Laser of Co2 + INF α -2a (high dose) Group.

Results in the 5-FU 5% Group were 29 patients and in the 5-FU 5% + Laser of Co2 + INF α -2a (high dose) Group was 1 patient.

In CA + CP group, 29 male patients were treated with 5-FU and 16 male patients were placed in 5-FU 5% + Laser of Co2 + INF α -2a (high dose) Group.

Results in the 5-FU 5% Group were 14 patients and in the 5-FU 5% + Laser of Co2 + INF α - 2a (high dose) Group were 3 patients.

Lesion recurrence observed inside the first year after treatment was considered as treatment failure.

Lesion recurrence occurred in all the 5-FU groups in months 3, 6 and 9.

Side effects were observed in 11% of the patients dealt with 5-FU.

8. CO2 Laser versus CO2 Laser + FU 5%

In that study, Carpinello et al., 1988, used a 5-FU 5% + CO2 Laser (compared with CO2 Laser without the 5 FU 5%, and 68 male patients were enclosed in the study, being 27 placed in the 5-FU + Co2 Laser Group and 41 patients placed in CO2 Laser Group.

The outcome studied was Lesion Recurrence (described even for only one lesion) and the results in the 5-FU Group + CO2 Laser were 19 patients and in the Co2 Laser Group were 28 patients.

DISCUSSION

The current therapies for condyloma and some in development are included under headings that relate its mechanism of the action, however, there is little knowledge between the differences in the mechanism of action of the antiviral therapy, that it only presumes acts in viruses components in response, and of the antiproliferative and antimitotic composites, that it believes to act in cellular targets. Despite of the little agreement, it is postulated that HPV infection can occasionally resolve spontaneously.

We observed in our research that there are few studies evaluating 5-FU for the treatment of the genital warts, and the majority of these are not randomised studies.

A problem observed in our research was the lack of homogeneity among the included studies, which, although few in number, presented a great number of comparisons, with varied outcomes and without a uniform sample at the time of our search, making meta-analysis difficult. This lack of homogeneity of the studies makes it difficult to make clinically useful evaluations of the results of the clinical assays.

The included studies for meta-analysis presented some important differences, such as variation in concentration of 5-FU. Another problem observed in this review was the quality of the studies. Four of the six studies had been classified as having moderate risk of bias Relakis 1996, Botacini 1993, Carpinelo 1988, Weismann 1982. Only two studies had been classified as having low risk of bias Syed 2000, Wallin 1977.

To diminish the problems of incomplete information in the articles, we tried to contact the main author of each study, but because the majority of the studies were older, it was not possible. Thus, doubts remain about methodological quality of those studies and the extent to which it could affect our review. The inclusion of poor studies in meta-analysis could cause us to underestimate or overestimate the results Schulz 1995 .

Due to the existence of few studies evaluating 5-FU in patients with condyloma, it was not possible to do sensitivity analysis to evaluate the heterogeneity observed in some analyses.

When the outcome considered was cure alone, 5-FU was superior to placebo, to MCSA and the Podophylin (Botacini 1993) showing that 5-FU can be a good option of treatment. When we considered only treatment failure/ no response as an outcome, we observed that 5-FU was superior to placebo, to MCSA, Podophylin 2% Botacini 1993 and CO2 Laser for condyloma treatment Relakis 1996 and inferior to 5-FU + INFα - 2a (low dose) Relakis 1996. THere was no statistical significance between the treatments of 5-FU + INFα - 2a (high dose) and 5-FU + Laser of Co2 + INFα - 2a (high dose) Relakis 1996. This

demonstrates that 5-FU is a good treatment option in view of the costs of INF α- 2a and the CO2 Laser.

In view of the search for a treatment that with easy application and low cost and considering the lack of quality studies that justified 5-FU in the treatment of genital warts, this review suggests that studies with small sample sizes could be grouped to demonstrate the effectiveness and safety of this drug in the treatment of genital warts.

In addition, the majority of the trials reviewed were of low quality and study design and methodology were heterogenous. Such heterogeneity represents a formidable hindrance to the pooling of data and descriptive synthesis of information. Within these trials there were a large number of important variables distinguishing them.

PARTICIPANT FACTORS

Age of the participants: as the studies do not evaluated participants for age band it is not possible to verify if there were differences in the results between younger and older patients.

TREATMENT FACTORS

Topical treatments: different concentrations from 5-FU, Podophylin and INF?-2a formulations

Trial period: different periods of treatment and different periods before outcome assessment.

STATISTICAL HETEROGENEITY

The heterogeneity of study designs and methodology described above meant that not many data could be pooled and subjected to meta-analysis. Where data were pooled, a random effects model was used for all comparisons.

PUBLICATION BIAS AND TRIAL SIZE

The limited nature of the meta-analyses in this review prevented any formal evaluation of publication bias with funnel plots.

Given our reservations about the quality and overall heterogeneity of the trials reviewed it is suggested that greater credence is given to the trials with larger numbers of people treated despite that they may show smaller treatment effects.

AUTHORS' CONCLUSIONS

Implications for practice

Despite of the limited evidences provided by the studies included in our review we believe that topical 5-FU can be used in selected cases. We also believe this weak evidence is due, in part, to the diverse and complex study designs and the lack of the similarity among them.

Implications for research

This review shows the need for high quality randomised controlled trials, with adequate research design or methodology, comparing various concentration of topical 5-FU and other drugs in the treatment of genital condyloma, with follow up adjusted for the evaluation of the outcomes: cure, side effects, treatment failures, and recurrence of lesions.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Botacini 1993

Study characteristics	
Methods	Parallel Randomized Controlled Trial, Category B, Jadad 1
Participants	Two hundred and fifty four women with HPV-infection whose diagnostic was done by colposcopy, Pap smear, and direct biopsy by colposcopy allocated into five groups: 1) control n=16 2) Podophylin 4%, n=5 3) Podophylin 2%, n=40 4) 5-Fluorouracil 5%, n=74 5) Meta-cresol-sulfonic acid, n=9
Interventions	Patients were randomised to five groups. 1) control (placebo) 2) Podophylin 4%, vaginal gel 5g in 15 applications in alternate days 3) Podophylin 2%, vaginal gel 5g in 15 applications in alternate days

Botacini 1993 *(Continued)*

	4) 5-fluorouracil 5%, 2 vaginal applications weekly for 8 weeks 5) Meta-cresol-sulfonic acid, in alternate days for 30 days
Outcomes	1) Cure - defined as negative of colposcopy, Pap smear, and direct biopsy by colposcopy. 2) Partial response/ improvement - defined as presence only of positive cytology for HPV infection 3) No response / resistance to the treatment - defined as not alteration of the warts, CIN development or aggravation of lesions to the end of the study
Notes	The follow-up was done by 12 weeks 110 patients were excluded in the course of treatment because they did not follow the protocol requirement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In accordance with the effected treatment patients had been divided randomly in five groups..." Comment: Probably not done because there was no indication of the method used to distribute the patients, and because of the great difference of the "n" in each group
Allocation concealment (selection bias)	Unclear risk	Quote:...patients had been divided randomly in five groups..." Comment: Probably not done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described Comment: Probably not done.

Carpinelo 1988

Study characteristics

Methods	Parallel Randomized Controlled Trial, Category B, Jadad "0"
Participants	Sixty-eight men, sexual partners of women with cervical dysplasia, cervical intraepithelial neoplasia (CIN), carcinoma in situ or severe Condylomatous atypia allocated into 2 groups:1) Group CO2 laser, n =41, and 2) Group 5-fluorouracil plus CO2 laser, n=27.
Interventions	1)CO2 Laser; 2)CO2 Laser plus adjuvant 5-FU 5% for 30 days beginning a week after the laser therapy
Outcomes	Recurrence of lesion described as any evidence of HPV (even 1 lesion) after treatment
Notes	Patients in the CO2 Group were followed for a mean of 4.1 months, while those in the CO2 Laser plus adjuvant 5-FU 5% were followed for a mean of 4.0 mouths

Risk of bias

Bias	Authors' judgement	Support for judgement

Carpinelo 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "All randomised 68 patients evaluated in this study received magnified penile surface-carbon dioxide laser therapy as described above. Of the patients 41 were treated with magnified penile surface-carbon dioxide laser therapy alone and 27 treated with a regimen of adjuvant 5 per cent 5-Fluorouracil applied to the penile shaft every other night for 1 month beginning 1 week after the laser therapy. Comment: Probably not done
Allocation concealment (selection bias)	Unclear risk	Quote: "All randomised 68 patients evaluated..." Comment: Probably not done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described Comment: Probably not done

Relakis 1996

Study characteristics	
Methods	Parallel Randomized Controled Trial. Category B, Jadad "0"
Participants	Five hundred and five men, sexual partners of women with flat condyloma(FC) or condyloma acuminatum(CA) or cervical intraepithelial neoplasia (CIN) who presented HPV lesions (histologically confirmed). The majority of the patients (61,84%) were aged between 12 and 30 years.
Interventions	**Condyloma Acuminatum (CA) Group** 1) Single dose of 5-Fu 5% cream every night in the condylomatous region for 5 days, and in case of no response, treatment continued for other 3 courses of 5 days (every course was followed by 5 days with no treatment) 2) CO2 Laser-vaporization 3) Combination of 5-FU Cream for 2 courses of 5 days followed by INF?-2a low dose(single dose of 1.5 x 10^6 IU, sub-q abdominally) for 6 consecutive days 4) Combination of 5-FU Cream for 2 courses of 5 days followed by CO2-laser vaporization and INF?-2a high dose(single dose of 3 x 10^6 IU, sub-q abdominally) for 6 consecutive days **Flat Condyloma (FC) Group** 1) Single dose of 5-FU 5% Cream 2) CO2 Laser-vaporization 3) Combination of 5-FU Cream for 2 courses of 5 days followed by CO2-Laser vaporization 4) Combination of 5-FU Cream for 2 courses of 5 days followed by INF?-2a low dose for 6 consecutive days 5) Combination of 5-FU Cream for 2 courses of 5 days followed by INF?-2a high for 6 consecutive days 6) Combination of 5-FU Cream for 2 courses of 5 days followed by CO2-Laser vaporization and INF?-2a high dose for 6 consecutive days **FC + CA Group** 1) Single dose of 5-FU 5% cream

Relakis 1996 *(Continued)*

	2) CO2 Laser-vaporization 3) Combination of 5-FU Cream for 2 courses of 5 days followed by CO2-Laser vaporization 4) Combination of 5-FU Cream for 2 courses of 5 days followed by CO2-Laser vaporization and INF ? -2a high dose for 6 consecutive days.
Outcomes	Failure of treatment defined as recurrence of lesions within first year
Notes	It were excluded from the study patients with a granulocyte count of < 2,000/ml or a platelet count < 100,000, patients with renal dysfunction as measured by a serum creatinine levels > 1,4 mg/ml, patients with serum glutamic oxaloacetic transaminase of > 120U, patients with total bilirubin level of > 2,0mg/dl, patients with symptoms of heart disease, chronic obstructive pulmonary disease, liver disease, malignancy, psychiatric disorders necessitating medications or any neurologic disorder, patients with human immunodeficiency virus seropositivity and patients with evidence of significant immunosuppression as determined by clinical evidence of opportunistic infection or treatment with immunosuppressive drugs, patients with known or presumed hypersensitivity to interferon or 5-FU, patients with previous gastrointestinal disorders, regular aspirin, LSD and heroin users and patients with any type of anaemia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"... of whom 505 were evaluated after treatment for FC or Ca or combination of FC and CA " Comment: Probably not done due to allocation had been done by HPV type
Allocation concealment (selection bias)	Unclear risk	Quote: "Three treatment groups were established: group A with CA (n=102) group B with FC (n= 325) and group C with a combination of FC an CA (n=78)" Comment: Groups were formed by HPV type
Blinding (performance bias and detection bias) All outcomes	High risk	Not done. Both Doctors and patients were not blinding concerning interventions

Syed 2000

Study characteristics

Methods	Parallel Randomizad Controlled Trial, Category A, Jadad 5
Participants	Sixty women aged over 17 years (ranging 18 and 50, mean of 24,6 years) with 312 intravaginal warts (mean of 5.2) allocated in 2 groups with 30 patient in each group
Interventions	5 FU 1% (4g) intravaginal 3 times in the week at bedtime for 4 weeks Placebo
Outcomes	Cure - defined as total condyloma regression with absence of clinic signals by colposcopic and negative PCR and Shoutern Blot for HPV Improvement - defined as 50% or more regression of lesions

Syed 2000 *(Continued)*

	Failure - defined as regression of less 50% of lesions Side effects - presence of erosion or edema or inflammation or local discomfort or dysuria or local hypersensitivity
Notes	It were excluded from the study pregnant women, nurses, external condyloma, malignant disease, known hypersensitivity to fluoride pirimidine or hidroxietilcelulose, HIV positive individuals, heart disease, liver disease, lung disease, renal disease, associated STD, use of immunosuppressive or antiviral drugs in the last 2 months or intravaginal medication 8 weeks prior to the selection for study Bicentric (USAand Paquistan) Follow-up period was of 16 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients enlisted for the study were randomly assigned to numbers 1-60 sequentially to receive either active or placebo gel treatment..." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: "Each patient had received a pre-code tube 15g (active or placebo) with graduated vaginal applicators (disposable), and instructions how to insert 4g of the trial medication deep into the vagina once a bedtime on every day (1,3,5) per week" Comment: Probably done due to description of the way it was performed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "In a double-blind manner, pre-coded trial preparation (15g), with graduated (4ml, correspond to 4g) vaginal applicators (disposable) were allocated to each patient." Comment: Probably done

Wallin 1977

Study characteristics

Methods	Parallel Randomized Controlled Trial, Ctegory A, Jadad 3
Participants	Forty two men with condyloma acuminata whose ages ranged between 19 and 36 years (mean 24 years) were allocated in two treatment groups that were described as similar in age, marital status, size of warts and warts distribution
Interventions	1) 5-FU Group - 5-FU cream 5% self-applied every night for 2 weeks, n=20 2) Podophyllin Group - Podophyllin 25% solution applied to the warts by the doctor once a week for four consecutive weeks, n=22
Outcomes	1) Failure - defined as total absence of response 2) Recurrence - defined as reappearance of lesions during treatment after a initial response, in the follow up 3) Cure - defined as disappearance of genital warts

Wallin 1977 *(Continued)*

Notes	Follow up was done by 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated in two treatment groups using a table of random numbers." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote: "...using a table of random numbers." Comment: Probably done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described Comment: Problaby not done

Weismann 1982

Study characteristics

Methods	Double Blind Parallel Randomization Controlled Trial, category B, Jadad "1"
Participants	Fifty nine patients (30 men and 29 women) with anogenital warts whose ages ranged between 21 and 36 yeas (mean 26,5 years) among men, and ages ranged between 17 and 38 years (mean 23,1 years) among women were randomised to two groups
Interventions	1) 5-FU Group - 5-FU 0,5% 2) Placebo
Outcomes	1) Cure - It was not described 2) Improvement - It was not described 3) No Response - It was not described
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients had been randomised for treatment using enamelum for vulgar warts with 0,5% 5-FU with Salicilic Acid to 10% and Dimethyl sulphoxide to 8% (Verrumal) or placebo (verrumal without 0,5% 5-FU)
Allocation concealment (selection bias)	Unclear risk	Not described Comment: Probably not done
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double Blind Parallel Randomization Controlled Trial" Comment: Probably done

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bergman	It is not RCT
Bringel	It is not RCT
Brodman	It is not RCT
Cardamakis	It is penile intraepithelial neoplasia
Cardamakis 1	It was not contact with author possible concerning randomisation.
Djawari	It is not RCT
Dretler	It is not RCT
Emokpare	It is not RCT
Ferenczy	It is not RCT
Halasz	It is not genital warts
Hursthouse	It is not genital warts
Husseinzadeh	It is use of 5-FU after treatment
Klutke	It is treatment of recurrent lesion with Interferon
Krebs	It is not RCT
Krebs 1	It is not RCT
Krebs 2	Include 2 immunosuppressed patients
Krebs 3	It is not RCT
Krebs 4	5-FU is used after one or treatment for preventing recurrence
Lopes	It is neither RCT nor Genital Warts
Moore	Inadequate methodology
Netto Junior	It is not RCT
Pride	It is not RCT
Schimidt	It is not genital warts
Stefanon	It is not RCT
von Krough	It is not RCT
Zarcone	It is not RCT

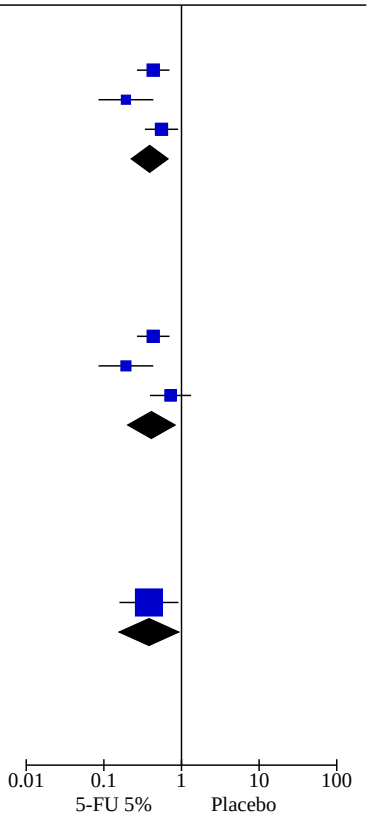
DATA AND ANALYSES

Comparison 1. 5-FU versus Placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Cure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Female plus Male	3	209	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.23, 0.67]
1.1.2 Female	3	179	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.20, 0.82]
1.1.3 Male	1	30	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.16, 0.91]
1.2 Cure for number of genital warts	1	312	Risk Ratio (M-H, Random, 95% CI)	6.22 [4.16, 9.28]
1.3 Partial Response / Melhora	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Female plus Male	1	59	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.17]
1.3.2 Female	1	29	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.47]
1.3.3 Male	1	30	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.17]
1.4 Absence of Response	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Female plus Male	1	59	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.16, 0.74]
1.4.2 Female	1	29	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.05, 0.69]
1.4.3 Male	1	30	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.22, 1.50]
1.5 Recurrence of Lesion	1	60	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.22]
1.6 Side Effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 5-FU 5% plus 1 %	2	150	Risk Ratio (M-H, Random, 95% CI)	13.23 [2.65, 65.96]
1.6.2 5-FU 5%	1	90	Risk Ratio (M-H, Random, 95% CI)	13.83 [0.89, 215.08]
1.6.3 5-FU 1%	1	60	Risk Ratio (M-H, Random, 95% CI)	11.00 [1.51, 79.96]

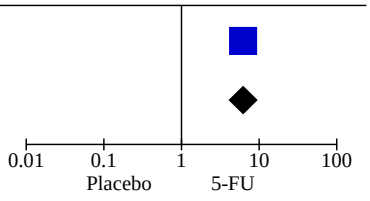
Analysis 1.1. Comparison 1: 5-FU versus Placebo, Outcome 1: Cure

Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
1.1.1 Female plus Male						
Botacini 1993	52	74	5	16	38.1%	0.43 [0.27 , 0.70]
Syed 2000	25	30	4	30	24.4%	0.19 [0.09 , 0.43]
Weismann 1982	18	30	8	29	37.5%	0.55 [0.34 , 0.90]
Subtotal (95% CI)		**134**		**75**	**100.0%**	**0.39 [0.23 , 0.67]**
Total events:	95		17			
Heterogeneity: Tau² = 0.14; Chi² = 5.28, df = 2 (P = 0.07); I² = 62%						
Test for overall effect: Z = 3.43 (P = 0.0006)						
1.1.2 Female						
Botacini 1993	52	74	5	16	37.7%	0.43 [0.27 , 0.70]
Syed 2000	25	30	4	30	28.3%	0.19 [0.09 , 0.43]
Weismann 1982	8	16	4	13	34.0%	0.72 [0.39 , 1.33]
Subtotal (95% CI)		**120**		**59**	**100.0%**	**0.41 [0.20 , 0.82]**
Total events:	85		13			
Heterogeneity: Tau² = 0.28; Chi² = 7.52, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 2.51 (P = 0.01)						
1.1.3 Male						
Weismann 1982	10	14	4	16	100.0%	0.38 [0.16 , 0.91]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**0.38 [0.16 , 0.91]**
Total events:	10		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.16 (P = 0.03)						



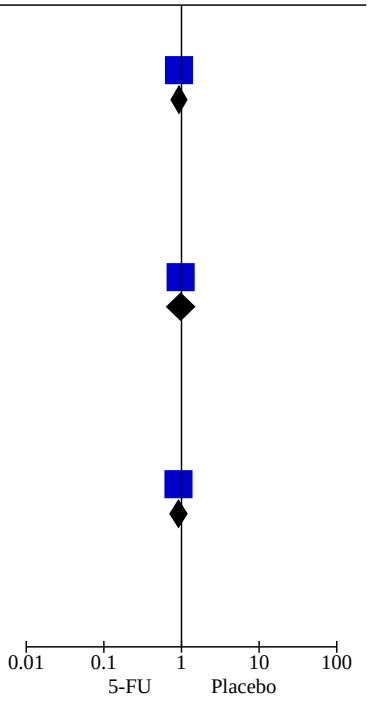
Analysis 1.2. Comparison 1: 5-FU versus Placebo, Outcome 2: Cure for number of genital warts

Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Syed 2000	141	162	21	150	100.0%	6.22 [4.16 , 9.28]
Total (95% CI)		**162**		**150**	**100.0%**	**6.22 [4.16 , 9.28]**
Total events:	141		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.93 (P < 0.00001)						
Test for subgroup differences: Not applicable						



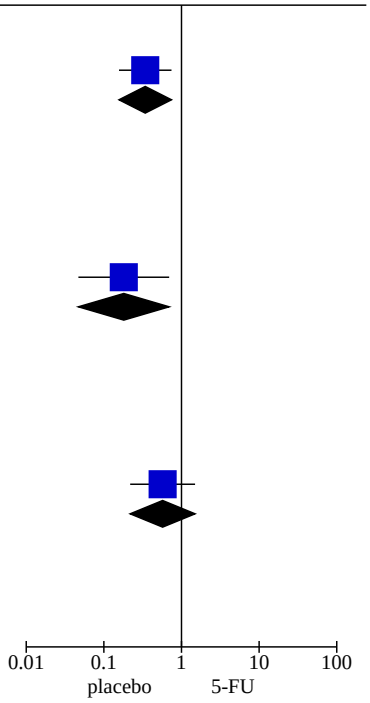
Analysis 1.3. Comparison 1: 5-FU versus Placebo, Outcome 3: Partial Response / Melhora

Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
1.3.1 Female plus Male						
Weismann 1982	6	30	4	29	100.0%	0.93 [0.74 , 1.17]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**0.93 [0.74 , 1.17]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.3.2 Female						
Weismann 1982	4	16	3	13	100.0%	0.97 [0.65 , 1.47]
Subtotal (95% CI)		**16**		**13**	**100.0%**	**0.97 [0.65 , 1.47]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
1.3.3 Male						
Weismann 1982	2	14	1	16	100.0%	0.91 [0.71 , 1.17]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**0.91 [0.71 , 1.17]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						



Analysis 1.4. Comparison 1: 5-FU versus Placebo, Outcome 4: Absence of Response

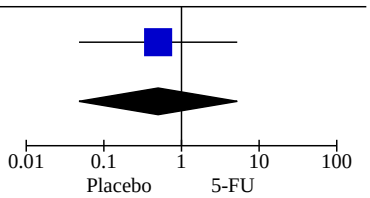
Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Female plus Male						
Weismann 1982	6	30	17	29	100.0%	0.34 [0.16 , 0.74]
Subtotal (95% CI)		**30**		**29**	**100.0%**	**0.34 [0.16 , 0.74]**
Total events:	6		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.71 (P = 0.007)						
1.4.2 Female						
Weismann 1982	2	16	9	13	100.0%	0.18 [0.05 , 0.69]
Subtotal (95% CI)		**16**		**13**	**100.0%**	**0.18 [0.05 , 0.69]**
Total events:	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.49 (P = 0.01)						
1.4.3 Male						
Weismann 1982	4	14	8	16	100.0%	0.57 [0.22 , 1.50]
Subtotal (95% CI)		**14**		**16**	**100.0%**	**0.57 [0.22 , 1.50]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						



Analysis 1.5. Comparison 1: 5-FU versus Placebo, Outcome 5: Recurrence of Lesion

Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Syed 2000	1	30	2	30	100.0%	0.50 [0.05 , 5.22]
Total (95% CI)		**30**		**30**	**100.0%**	**0.50 [0.05 , 5.22]**
Total events:	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: 5-FU versus Placebo, Outcome 6: Side Effects

Study or Subgroup	5-FU Events	5-FU Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 5-FU 5% plus 1 %						
Botacini 1993	41	74	0	16	34.4%	18.81 [1.22 , 290.87]
Syed 2000	11	30	1	30	65.6%	11.00 [1.51 , 79.96]
Subtotal (95% CI)		**104**		**46**	**100.0%**	**13.23 [2.65 , 65.96]**
Total events:	52		1			

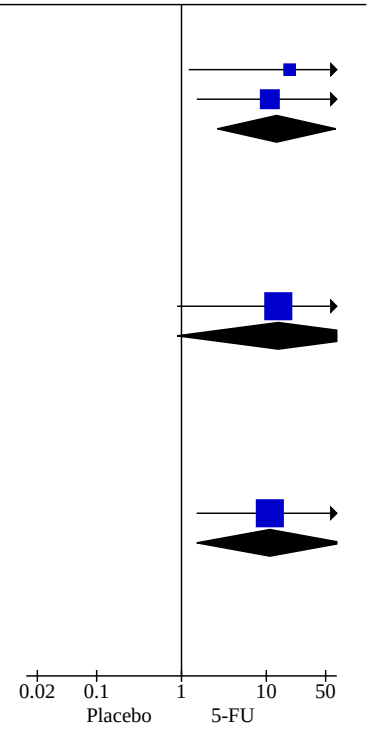
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 3.15 (P = 0.002)

1.6.2 5-FU 5%						
Botacini 1993	30	74	0	16	100.0%	13.83 [0.89 , 215.08]
Subtotal (95% CI)		**74**		**16**	**100.0%**	**13.83 [0.89 , 215.08]**
Total events:	30		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)

1.6.3 5-FU 1%						
Syed 2000	11	30	1	30	100.0%	11.00 [1.51 , 79.96]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**11.00 [1.51 , 79.96]**
Total events:	11		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)



Comparison 2. 5-Fu versus Meta-Cresol-Sulfonic Acid

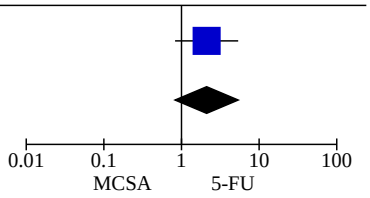
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Cure	1	83	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.83, 5.37]
2.2 Partial Response	1	83	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.09, 7.69]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.3 Absence of Response	1	83	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.17, 0.76]
2.4 Side Effects	1	83	Risk Ratio (M-H, Random, 95% CI)	8.13 [0.54, 122.90]

Analysis 2.1. Comparison 2: 5-Fu versus Meta-Cresol-Sulfonic Acid, Outcome 1: Cure

Study or Subgroup	5-FU Events	5-FU Total	MCSA Events	MCSA Total	Weight	Risk Ratio M-H, Random, 95% CI
Botacini 1993	52	74	3	9	100.0%	2.11 [0.83 , 5.37]
Total (95% CI)		**74**		**9**	**100.0%**	**2.11 [0.83 , 5.37]**
Total events:	52		3			

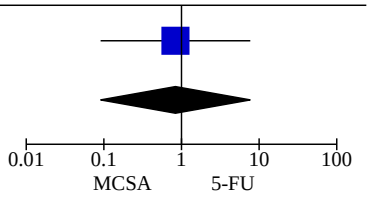
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: 5-Fu versus Meta-Cresol-Sulfonic Acid, Outcome 2: Partial Response

Study or Subgroup	5-FU Events	5-FU Total	MCSA Events	MCSA Total	Weight	Odds Ratio M-H, Random, 95% CI
Botacini 1993	7	74	1	9	100.0%	0.84 [0.09 , 7.69]
Total (95% CI)		**74**		**9**	**100.0%**	**0.84 [0.09 , 7.69]**
Total events:	7		1			

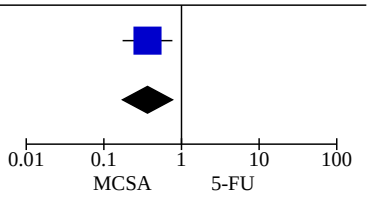
Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: 5-Fu versus Meta-Cresol-Sulfonic Acid, Outcome 3: Absence of Response

Study or Subgroup	5-FU Events	5-FU Total	MCSA Events	MCSA Total	Weight	Risk Ratio M-H, Random, 95% CI
Botacini 1993	15	74	5	9	100.0%	0.36 [0.17 , 0.76]
Total (95% CI)		**74**		**9**	**100.0%**	**0.36 [0.17 , 0.76]**
Total events:	15		5			

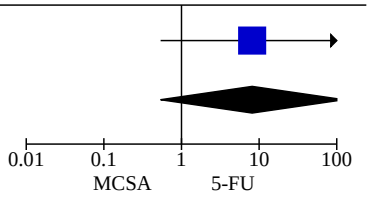
Heterogeneity: Not applicable
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: 5-Fu versus Meta-Cresol-Sulfonic Acid, Outcome 4: Side Effects

Study or Subgroup	5-FU Events	5-FU Total	MCSA Events	MCSA Total	Weight	Risk Ratio M-H, Random, 95% CI
Botacini 1993	30	74	0	9	100.0%	8.13 [0.54 , 122.90]
Total (95% CI)		**74**		**9**	**100.0%**	**8.13 [0.54 , 122.90]**
Total events:	30		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

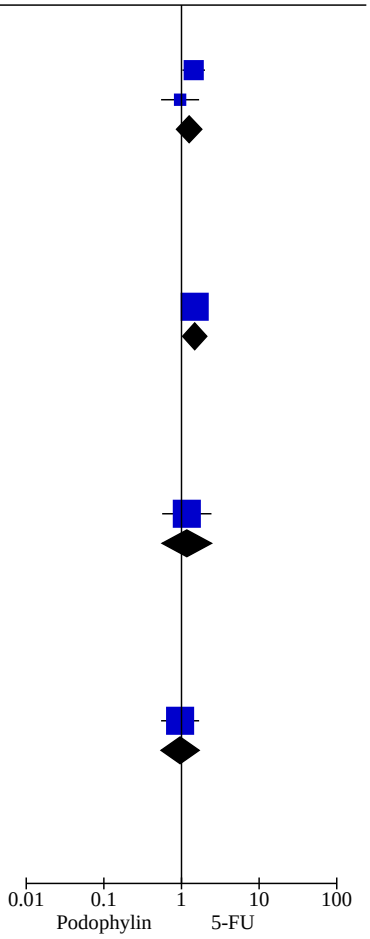


Comparison 3. 5-FU 5% versus Podophylin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Cure	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 Total cure	2	156	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.86, 1.82]
3.1.2 Podophylin 2%	1	114	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.03, 2.12]
3.1.3 Podophylin 4%	1	79	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.56, 2.43]
3.1.4 Podophylin 25%	1	37	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.55, 1.69]
3.2 Absence of Response	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Podophylin 2% plus Podophylin 4%	1	119	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.18, 0.96]
3.2.2 Podophylin 2%	1	114	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.16, 0.89]
3.2.3 Podophylin 4%	1	79	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.78]
3.3 Recurrence of Lesion	1	150	Risk Ratio (M-H, Random, 95% CI)	3.89 [2.29, 6.61]
3.4 Side Effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 2% plus 4%	1	119	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.99, 3.37]
3.4.2 Podophylin 2%	1	114	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.12, 4.79]
3.4.3 Podophylin 4%	1	79	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.31, 1.45]

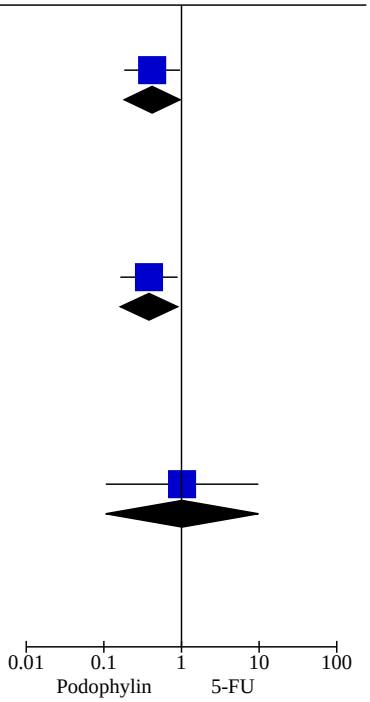
Analysis 3.1. Comparison 3: 5-FU 5% versus Podophylin, Outcome 1: Cure

Study or Subgroup	5-FU Events	5-FU Total	Podophylin Events	Podophylin Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Total cure						
Botacini 1993	52	74	22	45	66.4%	1.44 [1.03 , 2.01]
Wallin 1977	10	18	11	19	33.6%	0.96 [0.55 , 1.69]
Subtotal (95% CI)		**92**		**64**	**100.0%**	**1.26 [0.86 , 1.82]**
Total events:	62		33			
Heterogeneity: Tau² = 0.03; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 1.19 (P = 0.23)						
3.1.2 Podophylin 2%						
Botacini 1993	52	74	19	40	100.0%	1.48 [1.03 , 2.12]
Subtotal (95% CI)		**74**		**40**	**100.0%**	**1.48 [1.03 , 2.12]**
Total events:	52		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.14 (P = 0.03)						
3.1.3 Podophylin 4%						
Botacini 1993	52	74	3	5	100.0%	1.17 [0.56 , 2.43]
Subtotal (95% CI)		**74**		**5**	**100.0%**	**1.17 [0.56 , 2.43]**
Total events:	52		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.67)						
3.1.4 Podophylin 25%						
Wallin 1977	10	18	11	19	100.0%	0.96 [0.55 , 1.69]
Subtotal (95% CI)		**18**		**19**	**100.0%**	**0.96 [0.55 , 1.69]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						



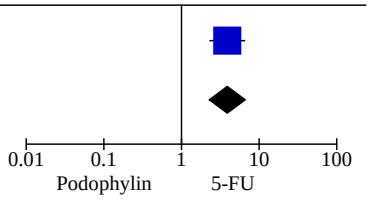
Analysis 3.2. Comparison 3: 5-FU 5% versus Podophylin, Outcome 2: Absence of Response

Study or Subgroup	5-FU Events	5-FU Total	Podophylin Events	Podophylin Total	Weight	Odds Ratio M-H, Random, 95% CI
3.2.1 Podophylin 2% plus Podophylin 4%						
Botacini 1993	15	74	17	45	100.0%	0.42 [0.18 , 0.96]
Subtotal (95% CI)		**74**		**45**	**100.0%**	**0.42 [0.18 , 0.96]**
Total events:	15		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						
3.2.2 Podophylin 2%						
Botacini 1993	15	74	16	40	100.0%	0.38 [0.16 , 0.89]
Subtotal (95% CI)		**74**		**40**	**100.0%**	**0.38 [0.16 , 0.89]**
Total events:	15		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
3.2.3 Podophylin 4%						
Botacini 1993	15	74	1	5	100.0%	1.02 [0.11 , 9.78]
Subtotal (95% CI)		**74**		**5**	**100.0%**	**1.02 [0.11 , 9.78]**
Total events:	15		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						

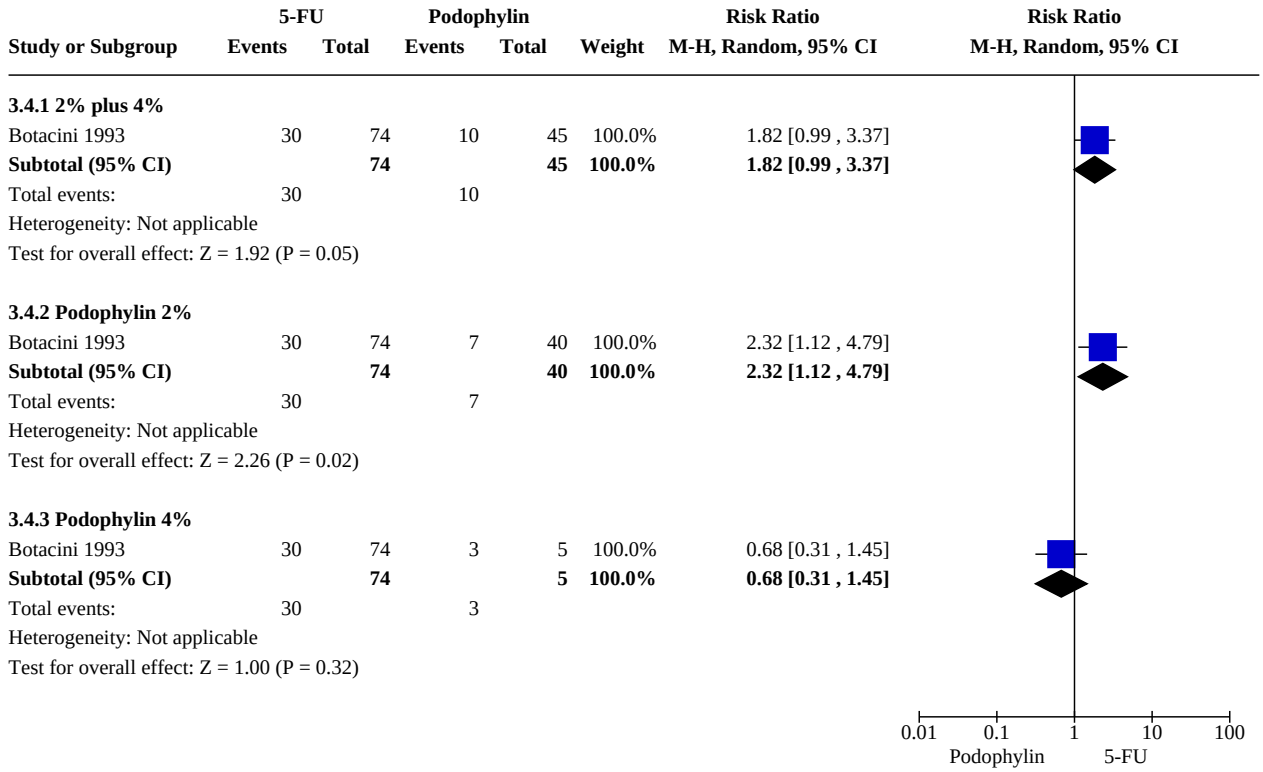


Analysis 3.3. Comparison 3: 5-FU 5% versus Podophylin, Outcome 3: Recurrence of Lesion

Study or Subgroup	5-FU Events	5-FU Total	Podophylin Events	Podophylin Total	Weight	Risk Ratio M-H, Random, 95% CI
Wallin 1977	83	99	11	51	100.0%	3.89 [2.29 , 6.61]
Total (95% CI)		**99**		**51**	**100.0%**	**3.89 [2.29 , 6.61]**
Total events:	83		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.02 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 3.4. Comparison 3: 5-FU 5% versus Podophylin, Outcome 4: Side Effects

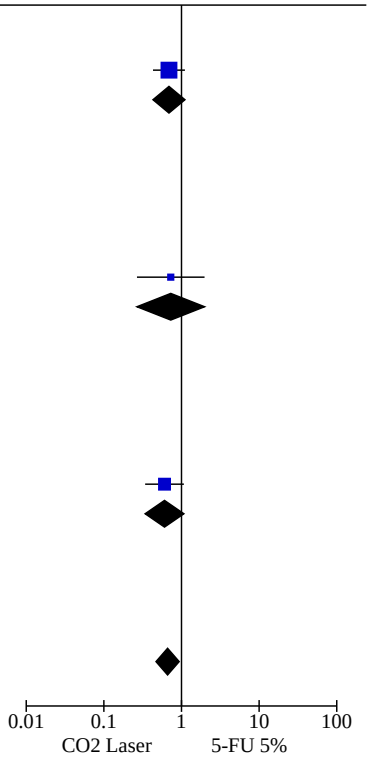


Comparison 4. 5-FU versus CO2 Laser

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Treatement failure	1	289	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.47, 0.93]
4.1.1 CA plus CP	1	49	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.43, 1.11]
4.1.2 CA	1	45	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.27, 1.98]
4.1.3 CP	1	195	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.07]

Analysis 4.1. Comparison 4: 5-FU versus CO2 Laser, Outcome 1: Treatement failure

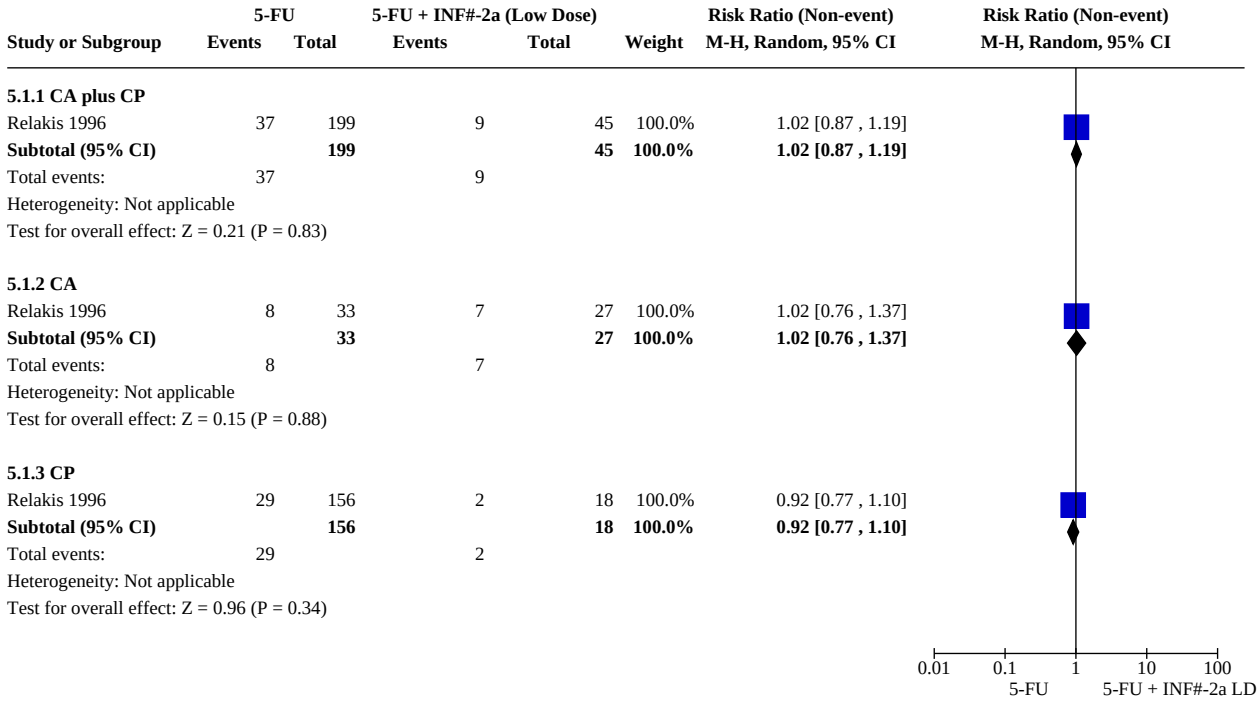
Study or Subgroup	5-FU 5% Events	5-FU 5% Total	CO2 Laser Events	CO2 Laser Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 CA plus CP						
Relakis 1996	14	29	14	20	52.5%	0.69 [0.43 , 1.11]
Subtotal (95% CI)		**29**		**20**	**52.5%**	**0.69 [0.43 , 1.11]**
Total events:	14		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
4.1.2 CA						
Relakis 1996	8	33	4	12	11.7%	0.73 [0.27 , 1.98]
Subtotal (95% CI)		**33**		**12**	**11.7%**	**0.73 [0.27 , 1.98]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
4.1.3 CP						
Relakis 1996	29	156	12	39	35.7%	0.60 [0.34 , 1.07]
Subtotal (95% CI)		**156**		**39**	**35.7%**	**0.60 [0.34 , 1.07]**
Total events:	29		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**218**		**71**	**100.0%**	**0.66 [0.47 , 0.93]**
Total events:	51		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
Test for subgroup differences: Chi² = 0.16, df = 2 (P = 0.92), I² = 0%						



Comparison 5. 5-FU versus 5-FU + INFα-2a (Low Dose)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Treatment Failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 CA plus CP	1	244	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.19]
5.1.2 CA	1	60	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.37]
5.1.3 CP	1	174	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.10]

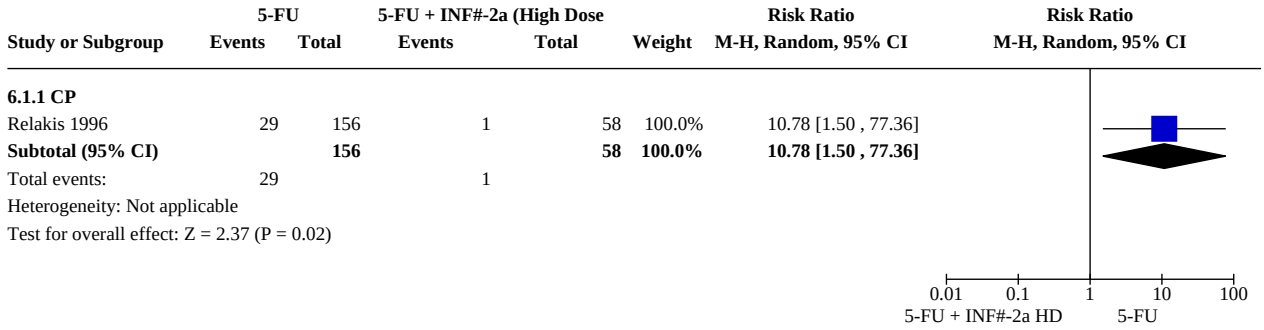
Analysis 5.1. Comparison 5: 5-FU versus 5-FU + INFα-2a (Low Dose), Outcome 1: Treatment Failure



Comparison 6. 5-FU versus 5-FU + INFα-2a (High Dose)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Treatment Failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 CP	1	214	Risk Ratio (M-H, Random, 95% CI)	10.78 [1.50, 77.36]

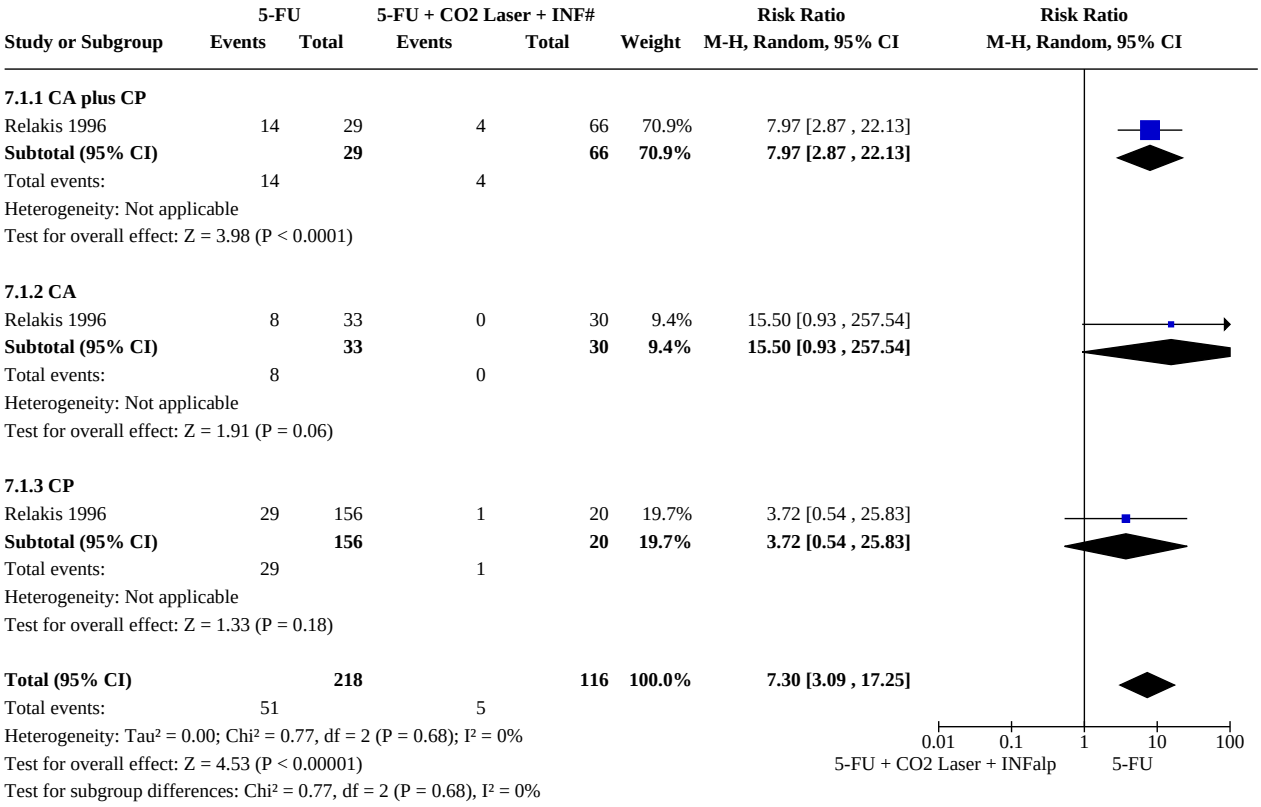
Analysis 6.1. Comparison 6: 5-FU versus 5-FU + INFα-2a (High Dose), Outcome 1: Treatment Failure



Comparison 7. 5-FU versus 5-FU + CO2 Laser + INFα-2a (High Dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Treatment Failure	1	334	Risk Ratio (M-H, Random, 95% CI)	7.30 [3.09, 17.25]
7.1.1 CA plus CP	1	95	Risk Ratio (M-H, Random, 95% CI)	7.97 [2.87, 22.13]
7.1.2 CA	1	63	Risk Ratio (M-H, Random, 95% CI)	15.50 [0.93, 257.54]
7.1.3 CP	1	176	Risk Ratio (M-H, Random, 95% CI)	3.72 [0.54, 25.83]

Analysis 7.1. Comparison 7: 5-FU versus 5-FU + CO2 Laser + INFα-2a (High Dose), Outcome 1: Treatment Failure



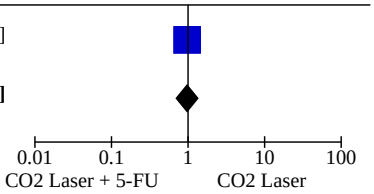
Comparison 8. CO2 Laser versus CO2 Laser + 5-FU 5%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Recurrence of Lesion	1	68	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.34]

Analysis 8.1. Comparison 8: CO2 Laser versus CO2 Laser + 5-FU 5%, Outcome 1: Recurrence of Lesion

Study or Subgroup	CO2 Laser Events	CO2 Laser Total	CO2 Laser + 5-FU Events	CO2 Laser + 5-FU Total	Weight	Risk Ratio M-H, Random, 95% CI
Carpinelo 1988	28	41	19	27	100.0%	0.97 [0.70 , 1.34]
Total (95% CI)		**41**		**27**	**100.0%**	**0.97 [0.70 , 1.34]**
Total events:	28		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Table 01 - Summary of the mechanisms of action of the used drugs for genital warts

DRUG	MECHANISM OF ACTION
5 - Fluoruracil (5-Fu)	Antimetabolic
Bichloroacetic or Trichloroacetic Acid	Tissue Chemical Destruction
Cryotherapy	Physical Freezing
Surgical Excision or Curettage	Surgical Removal
Cautery	Tissue Physical Destruction
Imiquimod	Immunomodulator
Interferon	Antiviral (immunomodulator)
CO2 Laser	Tissue Vaporization
Podophyllin	Antimitotic
Podophyllotoxin	Antimitotic
Vacinne	Antiviral (immunomodulator)

Adapted of: Schering Imiquimod Monograph. 2003

Table 2. Table 02 - Clinicians and researchers contacted

Name	Response	Additional RCTS?
Alex Ferenczy (CAN)	Yes	No
E.Cardamakis(Greece)	No	?

Table 3. Table 03- Pharmaceutical companies contacted

Name	Response	Additional RCTS?
ICN Farmacêutica Ltda	no	?

APPENDICES

Appendix 1. Data Collection Form

IDENTIFICATION

- Study ID (created by review author).
- Report ID (created by review author).
- Review author ID (created by review author).
- Citation and contact details.

METHODS

- Study design.
- Total study duration.
- Sequence generation*.
- Allocation sequence concealment*.
- Blinding*.
- Other concerns about bias*.

PARTICIPANTS

- Total number.
- Setting.
- Diagnostic criteria.
- Age.
- Sex.
- Country.
- [Co-morbidity].
- [Socio-demographics].
- [Ethnicity].
- [Date of study].

INTERVENTIONS

- Total number of intervention groups.

For each intervention and comparison group of interest:

- Specific intervention.
- Intervention details (sufficient for replication, if feasible).
- [Integrity of intervention].

OUTCOMES

- Outcomes and time points (i) collected; (ii) reported*.

For each outcome of interest:

- Outcome definition (with diagnostic criteria if relevant).
- Unit of measurement (if relevant).
- For scales: upper and lower limits, and whether high or low score is good.

RESULTS

- Number of participants allocated to each intervention group.

For each outcome of interest:

- Sample size.
- Missing participants*.
- Summary data for each intervention group (e.g. 2×2 table for dichotomous data; means and SDs for continuous data).
- [Estimate of effect with confidence interval; P value].
- [Subgroup analyses].

MISCELLANEOUS

- Funding source.
- Key conclusions of the study authors.
- Miscellaneous comments from the study authors.
- References to other relevant studies.
- Correspondence required.
- Miscellaneous comments by the review authors.

WHAT'S NEW

Date	Event	Description
22 April 2020	Review declared as stable	The 5-FU has been replaced and it is no longer used in general.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 4, 2010

Date	Event	Description
29 January 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

CLAUDIO SERGIO BATISTA - protocol development, selection of studies, quality assessment, data extraction, data analysis, review development

HUMBERTO SACONATO - protocol development, selection of studies, quality assessment, data extraction, data analysis, review development

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ÉDINA MARIKO KOGA DA SILVA - data extraction, data analysis, review development

DECLARATIONS OF INTEREST

No declaring

SOURCES OF SUPPORT

Internal sources

- none, Other

External sources

- none, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Combined Modality Therapy [methods]; Condylomata Acuminata [*drug therapy]; Cresols [administration & dosage]; Fluorouracil [*administration & dosage]; *Immunocompetence; Immunosuppressive Agents [*administration & dosage]; Interferon alpha-2; Interferon-alpha [administration & dosage]; Lasers, Gas [therapeutic use]; Podophyllotoxin [administration & dosage] [analogs & derivatives]; Randomized Controlled Trials as Topic; Recombinant Proteins; Sulfonic Acids [administration & dosage]

MeSH check words

Female; Humans; Male