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The Differences In Efficacy Between Human Papillomavirus Vaccine And Intralesional Cidofovir In Patients With Recurrent Respiratory Tract Papilloma Based On Derkay Score, Interval And Number Of Operations (Meta-Analysis)

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Abstract

Introduction: *Several adjuvant therapies have been used after surgery to reduce the recurrence in recurrent respiratory tract papilloma (RRP). To date, there is no adjuvant therapy that is consistently effective in reducing RRP recurrence. The older adjuvant therapy is intralesional cidofovir, and the newer is the HPV vaccine. The Derkay score is used to assess the clinical and therapeutic response of RRP. Lengthening of the operative interval and decreasing the number of surgeries are indicators of successful RRP adjuvant therapy.*

Objective: *Proving the efficacy of the HPV vaccine in patients with RRP compared to intralesional cidofovir based on the Derkay score, surgery interval, and number of surgeries.*

Method: *The meta-analysis study used the electronic databases PubMed, Science direct, Cochrane library, and Research gate. The efficacy of adjuvant therapy was assessed by Derkay score, surgery interval, and number of surgeries. The study steps were displayed in PRISMA 2020 flow and data analysis used RevMan 5.4.*

Result: *Sixteen cohort articles met the eligibility criteria. HPV vaccine adjuvant therapy significantly reduced Derkay score (SMD -1.15; CI 95% -2.27 until -0.03; p=0.004; I2=75%), extend the operation interval (SMD 0.77; CI 95% 0.20 until 1.3; p=0.008; I2=63%), and lower the number of operations (SMD -1.67; CI 95% -2.31 until -1.04; p<0.00001; I2=57%). Intralesional cidofovir adjuvant therapy did not significantly prolong the operative interval (SMD 0.25; CI 95% -0.21 until 0.72; p=0.28; I2=49%) and lower the number of operations (SMD -0.21; CI 95% -1.40 until 0.97; p=0.72; I2=84%), significantly lowered the Derkay score (SMD -1.24; CI 95% -2.24 until -0.24; p=0.02; I2=73%)..*

Conclusion*: HPV vaccine efficacy was shown to be equally effective in reducing Derkay scores compared to intralesional cidofovir in patients with RRP. HPV vaccine efficacy was shown to better prolong the interval and decrease the number of surgeries compared to intralesional cidofovir in patients with RRP.*

Keywords*: respiratory papillomatosis, HPV, vaccine, cidofovir, Derkay score, human and health disease.*

Introduction

Recurrent respiratory papillomatosis (RRP) is a benign tumor of the respiratory tract caused by human papilloma virus (HPV) types 6 and 11, with recurrent growth characteristics [1]. The current main treatment for RRP is surgery. Most patients with RRP require repeated surgical therapy over many years [2]. Repeated RRP surgery can lead to significant scarring, irreversible damage to the vocal cord, and respiratory dysfunction.[4] Repeated surgical procedures may lead to a decrease in the patient's quality of life. [5].

Several adjuvant therapies have been used after surgery to reduce recurrence, prolong the symptom-free interval, and decrease the number of surgeries in RRP [5]. Past adjuvant therapies include intralesional cidofovir and more

recently the HPV vaccine. To date, there is no adjuvant therapy that is consistently effective in reducing RRP recurrence. The efficacy of adjuvant therapy is still questionable because there are variable therapeutic results in patients with RRP [6]. The most prevalent causes of RRP are HPV types 6 and 11, which are also commonly detected in the anogenital area.[7],[8] Numerous biomarkers are being investigated to ascertain how they affect the aggressiveness of the disease. [9]

The Derkay score was developed to assess disease severity, clinical course, and response to RRP therapy over time [10]. The Derkay score is a scoring system for assessing the location and size of tumors as well as the clinical course of RRP [11]. Lengthening the operative interval and decreasing the number of operations have been used as indicators of the success of RRP adjuvant therapy. The surgical interval was determined by the surgeon at the time of the laryngoscopy. The decision of when to perform the next surgery is based on the tumor size, tumor extension, patient's clinical condition, previous surgery interval, patient's age, and the use of adjuvant therapy. The use of adjuvant therapy is associated with a longer time to the next RRP surgery [12]. Until now there are no research journals that compare the efficacy of HPV vaccines with intralesional cidofovir as adjuvant therapy in patients with RRP. The aim of this study was to prove the efficacy of the HPV vaccine in patients with RRP compared with intralesional cidofovir based on the Derkay score, surgery interval, and number of operations.

Method

This research is a meta-analysis. The research problem was described in the formulation of questions using the population, intervention, comparison, outcome, and study design (PICOS). Article searches used electronic databases PubMed, Science Direct, Cochrane Library, and Research gate with 3 months ending on December 31, 2022. The timing of the selected research articles was not limited to a specific period. Research articles were selected based on the inclusion, exclusion, and critical appraisal criteria using the Newcastle-Ottawa Scale (NOS) for cohort studies. The inclusion criteria are research subjects with RRP confirmed by histopathology results, adjuvant therapy given is a vaccine containing HPV types 6 and 11 in the form of a quadrivalent or nonvalent vaccine, adjuvant therapy given intralesional cidofovir injection, papilloma surgery performed with any tool and surgical technique, cohort study research design, data displaying mean ± standard deviation (SD) or mean, upper and lower confidence interval limits, and sample size. Exclusion criteria included review articles, case-control studies, case series, cross-sectional studies, incomplete data, full manuscripts that could not be downloaded, and research articles other than English and Indonesian. The research steps are displayed in the Prefers Reporting Items for Review and Meta-Analysis (PRISMA) 2020 flow diagram and data analysis using review manager software (RevMan) 5.4.

Result

The article search obtained 562 research articles, filtered 540 research articles. The next step, 22 research articles were obtained according to the inclusion criteria, and continued in the critical appraisal stage. The results of articles that have been carried out critical appraisal obtained 16 research articles that are eligible for data analysis. Six articles with a Derkay score outcome of 33 subjects in the HPV vaccine group and 30 subjects in the intralesional cidofovir group. Nine articles with an outcome of surgery interval of 88 subjects in the HPV vaccine group and 98 subjects in the intralesional cidofovir group. Nine articles with the outcome of the number of surgeries per year were 87 subjects in the HPV vaccine group and 38 subjects in the intralesional cidofovir group. Follow-up in these studies ranged from 24 months to 120 months.

Forest plot outcome Derkay score vaccine HPV I^2=75% with CI 95% p=0.04 which was statistically significant and in intralesional cidofovir I^2=73 with CI 95% p=0.02 which is statistically significant (Table 1).

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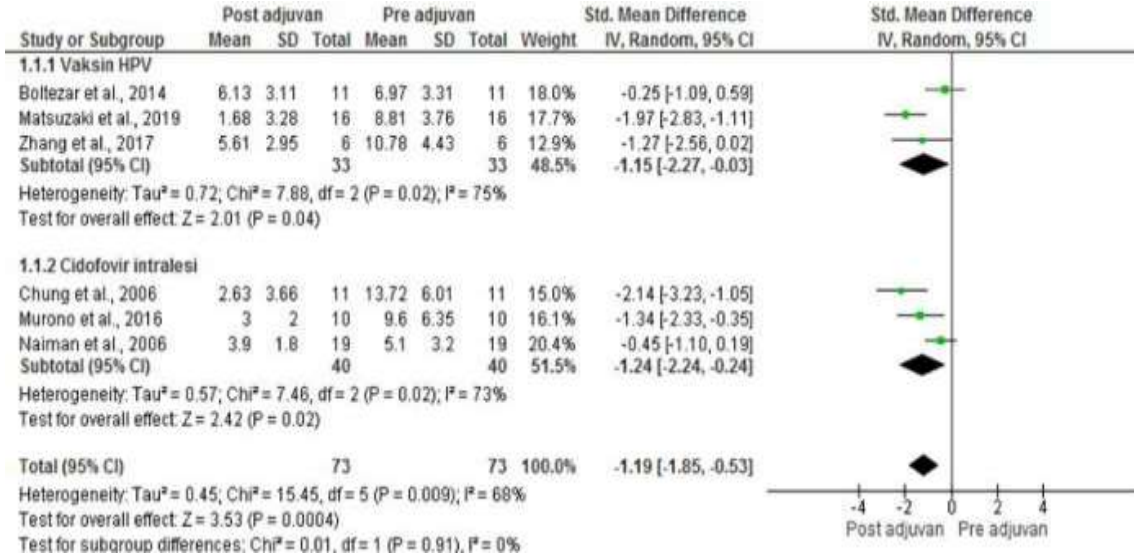
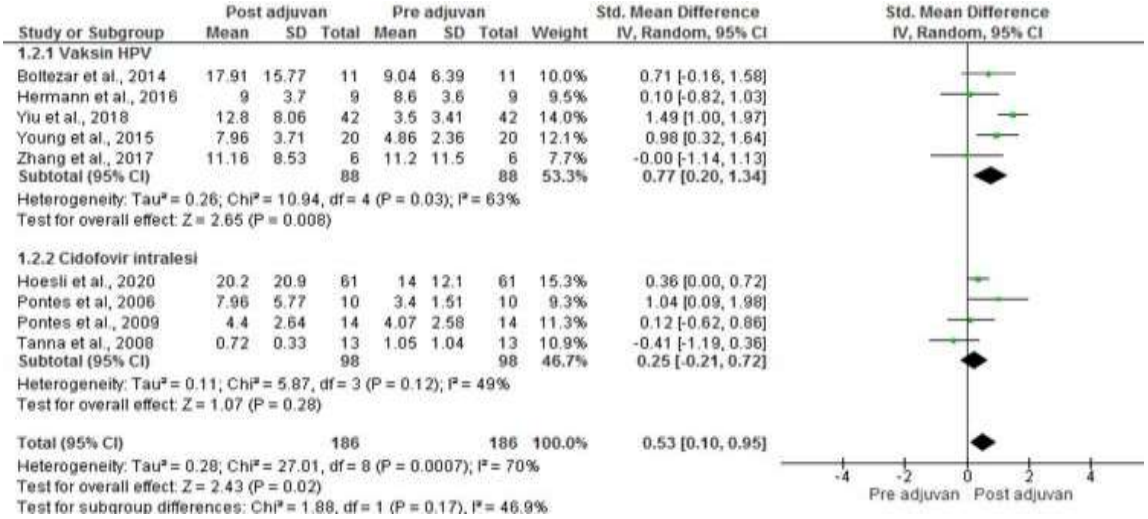
Tabel 1. Forest plot of HPV vaccine efficacy against RRP versus intralesional cidofovir based on Derkay score.



Forest plot of outcome of surgery interval obtained for HPV vaccine I^2=63% with CI 95% p=0.008 which was statistically significant and in intralesional cidofovir I^2=49% with CI 95% p=0.28 which is not statistically significant (Table 2).

Table 2. Forest plot of HPV vaccine efficacy against RRP versus intralesional cidofovir by surgery interval.



Forest plot of outcome of number of surgeries obtained for HPV vaccine I^2=57% with CI 95% p<0.00001 which was statistically significant and in intralesional cidofovir I^2=84% with CI 95% p = 0.72 which is not statistically significant (Table 3).

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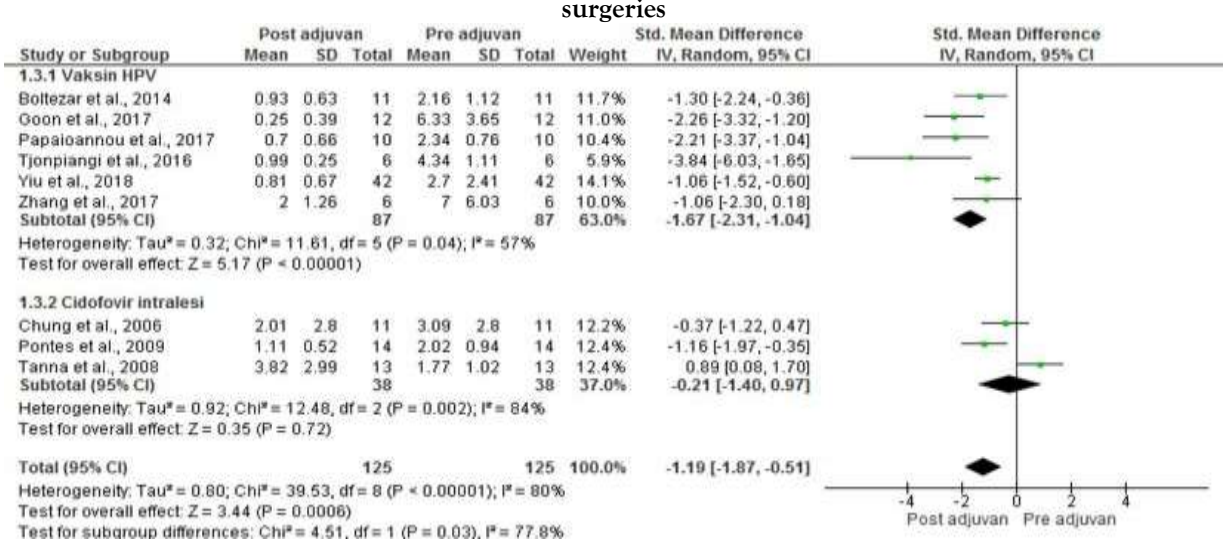
Table 3. Forest plot of HPV vaccine efficacy against RRP versus intralesional cidofovir by number of surgeries



Discussion

Articles that present Derkay scores on outcome assessment are 6 articles with details of 3 articles using HPV vaccine adjuvant therapy and 3 articles using intralesional cidofovir adjuvant therapy. The combined overall value of HPV vaccine adjuvant therapy illustrated in the forest plot in the over all effect test results showed a p value of 0.04, meaning that there was a significant decrease in Derkay scores after the administration of the adjuvant therapy. The combined overall score of the administration of intralesional cidofovir adjuvant therapy illustrated in the Forest plot in the over all effect test results showed a p value of 0.02, meaning that there was a significant decrease in Derkay's score after the administration of the adjuvant therapy.

Recurrence of RRP is caused by reinfection of HPV released from unresected non tumor areas at the time of surgery. Antibodies mediated by humoral and adaptive immune responses to HPV vaccines can inhibit latent HPV infection in the mucosa around the surgical site, thereby reducing the risk of reinfection and recurrence. HPV antibodies generated by HPV vaccine administration move from the blood vessels to tissues in the respiratory tract. HPV antibodies can neutralize HPV virions and prevent their binding to the basal cells of the respiratory tract [13]. HPV antibodies secreted into the respiratory tract suppress reinfection at the site of previous papilloma resection. The therapeutic effect of HPV vaccine adjuvant therapy is equivalent to that of intralesional cidofovir adjuvant therapy [14]. Cidofovir inhibits viral DNA polymerase, which is responsible for replication of new viral DNA. The active metabolite of cidofovir is cidofovir diphosphate, which selectively and competitively inhibits the incorporation of deoxycytidine triphosphate into viral DNA, thus inhibiting HPV replication [15]. These two RRP adjuvant therapies can reduce the severity and clinical status of RRP patients after surgery. The decrease in Derkay score after administration of HPV vaccine adjuvant therapy or intralesional cidofovir indicates an improvement in disease severity, the clinical course of RRP patients, and a positive response to these two RRP adjuvant therapies.

There were 9 articles that presented the surgery interval in the outcome assessment, 5 articles using HPV vaccine adjuvant therapy and 4 articles using intralesional cidofovir adjuvant therapy. The combined overall value of HPV vaccine adjuvant therapy illustrated in the forest plot in the overall effect test results showed a p-value of 0.008, indicating that there was a significant lengthening of the surgery interval after the administration of adjuvant therapy. The combined value of the overall administration of intralesional cidofovir adjuvant therapy depicted in the Forest plot in the overall effect test results showed a p-value of 0.28, indicating that there was no significant lengthening of the postoperative interval.

Sample size of various research articles affects the quality of meta-analysis results [16]. Differences in protocols for dose, frequency of administration, number of injections and drug concentration may affect therapeutic efficacy [17]. There was a lack of uniformity in the dose of intralesional cidofovir used in some of the primary articles in this study. This may affect the difference in efficacy between the two adjuvant therapies.

Articles that presented the number of operations in the outcome assessment were 9 articles with details of 6 articles using HPV vaccine adjuvant therapy and 3 articles using intralesional cidofovir adjuvant therapy. The combined overall value of HPV vaccine adjuvant therapy illustrated in the Forest plot in the over all effect test results showed a p value <0.00001, meaning that there was a significant decrease in the number of operations per year after the administration of the adjuvant therapy. The combined value of the overall administration of intralesional cidofovir adjuvant therapy depicted in the Forest plot in the over all effect test results showed a p value of 0.72, meaning that there was no significant decrease in the number of operations per year after the administration of the adjuvant therapy.

HPV vaccine adjuvant therapy can significantly reduce the number of operations per year, while in intralesional cidofovir, there was no significant difference before and after adjuvant therapy in patients with RRP. Decreasing the number of operations improves the quality of life of patients with RRP [18]. Immunodeficiency conditions prevent effective clearance of HPV 6 and HPV 11 and control of RRP [19]. The immune status of each patient with RRP has not been examined in several studies; therefore, the difference in HPV antibody concentration may cause differences in the efficacy of adjuvant therapy. The lack of efficacy of intralesional cidofovir may be due to the differences in the surgical techniques used. There are differences in the surgical techniques used in several research articles, which can affect the results of the administration of intralesional cidofovir adjuvant therapy, causing differences in efficacy.

The limitation of this study is that articles examining direct comparison of HPV vaccine and intralesional cidofovir have not been conducted. Another limitation was the use of three outcome variables that were not present in one research article. The limitations of the search strategy based on the specified keywords and the search for research articles using only four electronic databases may also affect the research articles obtained.

Conclusion

HPV vaccine efficacy was shown to be equally good at reducing Derkay scores compared to intralesional cidofovir in patients with RRP. HPV vaccine efficacy was shown to better prolong the interval and decrease the number of surgeries compared to intralesional cidofovir in patients with RRP.

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Conflict of Interest

The researcher declares no conflict of interest in the publication of this article.

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